The American Journal of

CARDIOLOGY

OFFICIAL JOURNAL OF THE American College of Cardiology

Radioelectrocardiography

A PUBLICATION OF THE Yorke GROUP

SEPTEMBER 1961

Isordil produces a dramatic decrease in the incidence and severity of Angina Pectoris[1]

- fourteen papers published within the past year document this therapeutic advance.

Isordil "...appears to exert a more consistent and profound effect than any drug previously used for the prophylaxis of angina pectoris."[1] Rapid onset of action and prolonged effect are important advantages over other agents. "Benefits from [Isordil therapy] seemed to be more marked with continued use."[1]

Other studies have shown similar striking results.[2-7] With Isordil, you can expect a "...substantial reduction in frequency and duration of [angina] attacks."[2] Nitroglycerin requirements often can be drastically reduced or eliminated.

why Isordil is different

- With its high solubility, comparable to that of nitroglycerin, Isordil has a much faster onset of action than do some older therapies. For example, with Isordil the therapeutic lag caused by the low solubility of PETN is avoided. Isordil starts to work within 15 to 30 minutes; as fast as two minutes if partially dissolved in the mouth before swallowing.

- Because the liver metabolizes it very slowly, Isordil has a longer duration of action—about 4 to 6 hours.

References: 1. Albert, A.: Isosorbide Dinitrate in Treatment of Angina Pectoris, Journal Lancet 81:112 (Mar.) 1961. 2. Shapiro, S.: Angina Pectoris: Treatment with Isosorbide Dinitrate, Angiology 12:53 (Feb.) 1961. 3. Leslie, R. E.: Coronary Vasodilators—A Comparative Study, Western Medicine 2:56 (Feb.) 1961. 4. Russek, H. I.: Comparative Responses to Various Nitrates in the Treatment of Angina Pectoris, Journal of the Kansas City Southwest Clinical Society 36:14 (Dec.) 1960. 5. Berry, J. W.; Carney, R. and Lankford, H.: Clinical Experiences with Isosorbide Dinitrate (Isordil®), Angiology 12:254 (June) 1961. 6. Sherber, D. A. and Gelb, I. J.: The Clinical Pharmacology of Isosorbide Dinitrate: A Unique, New Nitrated Polyalcohol, ibid. 7. Joseph, L. G. and Mancini, A.: Isosorbide Dinitrate in Angina Pectoris, ibid.

Reprints, literature and professional samples available on request. Consult direction circular or Physicians' Desk Reference before prescribing.

FOR ANGINA PECTORIS

Isordil®

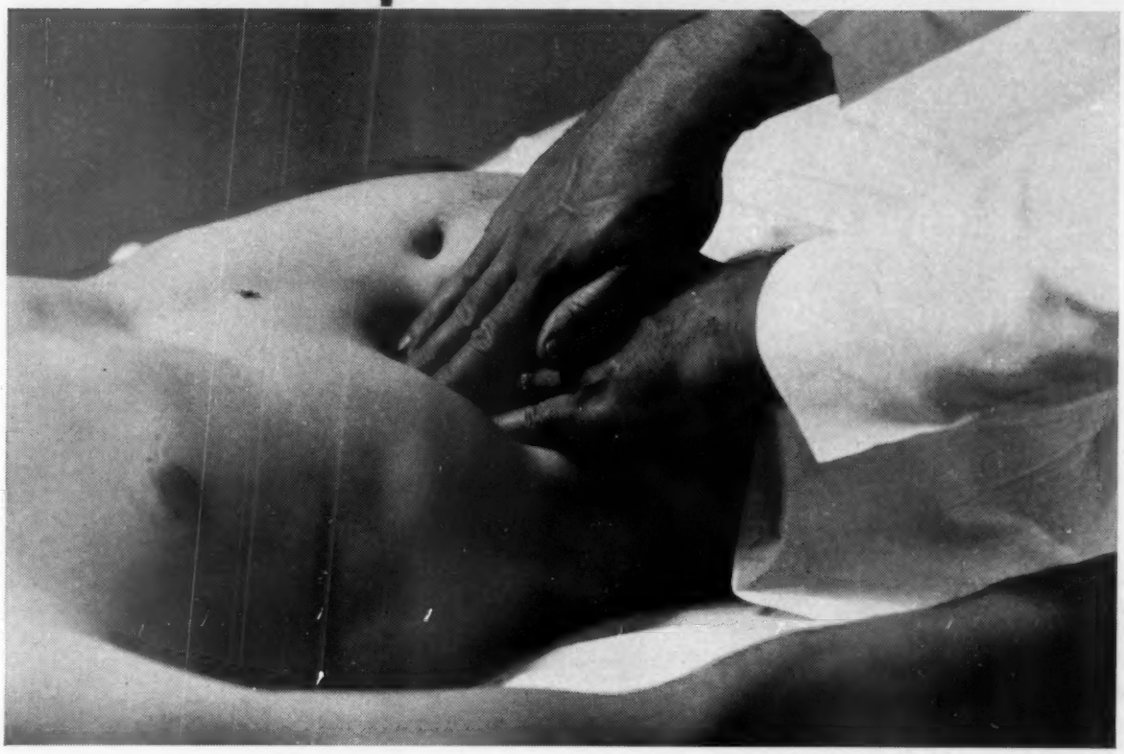
(ISOSORBIDE DINITRATE)

Also Available: ISORDIL WITH PHENOBARBITAL, the accepted sedative for the relief of anxiety in heart patients.

IVES-CAMERON COMPANY, New York 17, N. Y. IVES

*Trademark

in hepatic cirrhosis



ALDACTONE®

may prolong life...restore patients to productive capacity

Aldactone, which has demonstrated its ability to relieve resistant cardiac edema and ascites, has been found particularly effective in relieving the edema of hepatic cirrhosis.

The consistently high level of urinary aldosterone and aldosterone secretion rates in cirrhotic patients indicate that excessive production of this potent salt-retaining hormone is a major factor in their retention of fluid. As a selective aldosterone blocker, Aldactone may be relied on to relieve aldosterone-induced edema and ascites.

Clowdus and his co-workers[1] gave Aldactone to eight cirrhotic patients whose condition had failed to respond to salt restriction and conventional diuretics used singly and in combination. All responded satisfactorily when Aldactone was added to their therapeutic regimen.

In summarizing their experience with Aldactone these investigators state: "Aldactone, in conjunction with other diuretics and dietary sodium restriction, produced a striking and sustained diuresis in each of eight patients with ascites that had previously been refractory to treatment."

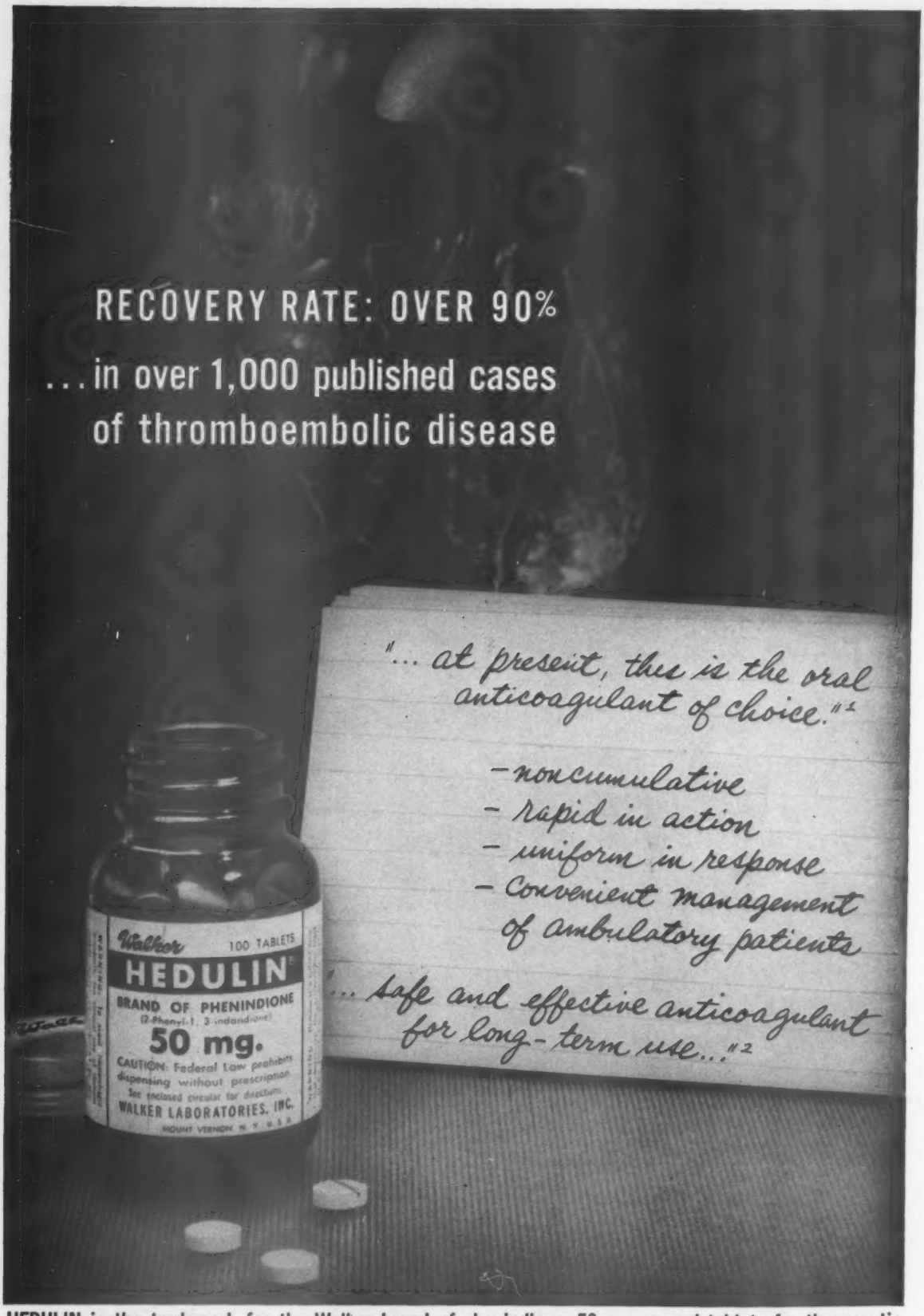
Indications: Edema and ascites associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome and idiopathic edema.

Dosage and Supply: To take advantage of a highly useful synergism and to secure immediate optimal diuresis, Aldactone should ordinarily be administered with a full dosage of a thiazide diuretic. The recommended adult dosage of Aldactone, alone or in combination, is 100 mg. four times daily. As much as 1,200 mg. may be given daily but will rarely be necessary. Aldactone should be administered cautiously to patients with hyponatremia or hyperkalemia, and potassium supplementation should not be used. Aldactone is supplied as compression-coated yellow tablets of 100 mg.

1. Clowdus, B. F.; Higgins, J. A.; Rosevear, J. W., and Summerskill, W. H. J.: Treatment of "Refractory" Ascites with a New Aldosterone Antagonist in Patients with Cirrhosis, Proc. Staff Meet. Mayo Clin. *35*:97 (March 2) 1960.

G. D. SEARLE & CO., CHICAGO 80, ILLINOIS

Research in the Service of Medicine



HEDULIN is the trademark for the Walker brand of phenindione. 50 mg. scored tablets for therapeutic use; 20 mg. scored tablets for prophylactic use. Bottles of 100 and 1,000. For more detailed information and a clinical trial supply of Hedulin, write to Walker Laboratories, Inc., Mount Vernon, N. Y.

1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

Symbol of Distinguished Journalism

The American Journal of Cardiology

THE AMERICAN JOURNAL OF CARDIOLOGY is published monthly by The Reuben H. Donnelley Corporation, Executive and Editorial Offices, 466 Lexington Avenue, New York 17, N. Y. September 1961, Volume 8, No. 3. Publication Office, 20th and Northampton Streets, Easton, Pa. Second-class postage paid at Easton, Pa. Official Journal of the American College of Cardiology.

SUBSCRIPTIONS: United States $12.00 a year; Canada $13.00; Foreign $15.00
SINGLE COPIES: Regular Issues $2.00; Symposium and Special Issues $4.00

MAIL CHANGES OF ADDRESS AND SUBSCRIPTION ORDERS TO: The American Journal of Cardiology, 466 Lexington Avenue, New York 17, N. Y. Change of address must reach us one month in advance.

MANUSCRIPTS: All manuscripts should be typewritten double space and submitted in duplicate to the Editorial Office of The American Journal of Cardiology, 466 Lexington Avenue, New York 17, N. Y. The top should be indicated on the back of each photograph. Reference style: Smith, J. S. Treatment of cardiac failure. *Am. J. Cardiol.*, 3: 274, 1959.

AMERICAN COLLEGE OF CARDIOLOGY: All communications for the College except manuscripts should be addressed to the American College of Cardiology, Office of the Executive Director, 350 Fifth Ave., New York 1, N. Y.

PLINY A. PORTER—Publisher
JOHN J. MARTIN—Assistant Publisher

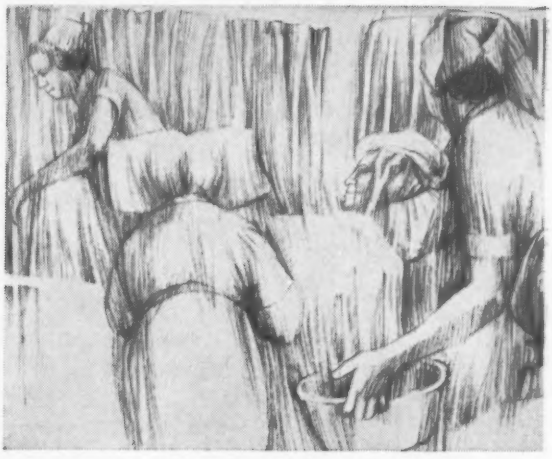
New Alvodine®

Brand of piminodine ethanesulfonate *ethanesulfonate*

An analgesic for

1. Ambulatory patients.

Whenever codeine or codeine-aspirin combinations are used, Alvodine taken orally can relieve pain better without dulling mental acuity or enervating the patients.



2. Postoperative patients.

Alvodine injected parenterally is as potent as morphine, but unlike morphine, it permits patients to remain alert postoperatively. It favors early mobilization of patients because it is usually not hypnotic.

3. Cancer patients.

Alvodine produces relief without weakening the cancer patient. Alvodine allows patients to eat normally, to maintain their strength and to continue their day-to-day activities to the extent permitted by their disease.

Alvodine is the first narcotic analgesic with action approaching "pure" analgesia. It relieves pain without producing sedation, drowsiness or drugged sensation.* This unique characteristic makes Alvodine the most desirable agent for pain relief in these three large groups of patients.

Alvodine Tablets, 50 mg., scored.
Alvodine ampuls, 1 cc. containing 20 mg. per cc.
Narcotic blank required.
Write for detailed information on clinical experience, addiction liability, side effects and precautions.

*In more than 90% of patients

Winthrop LABORATORIES
New York 18, N.Y.

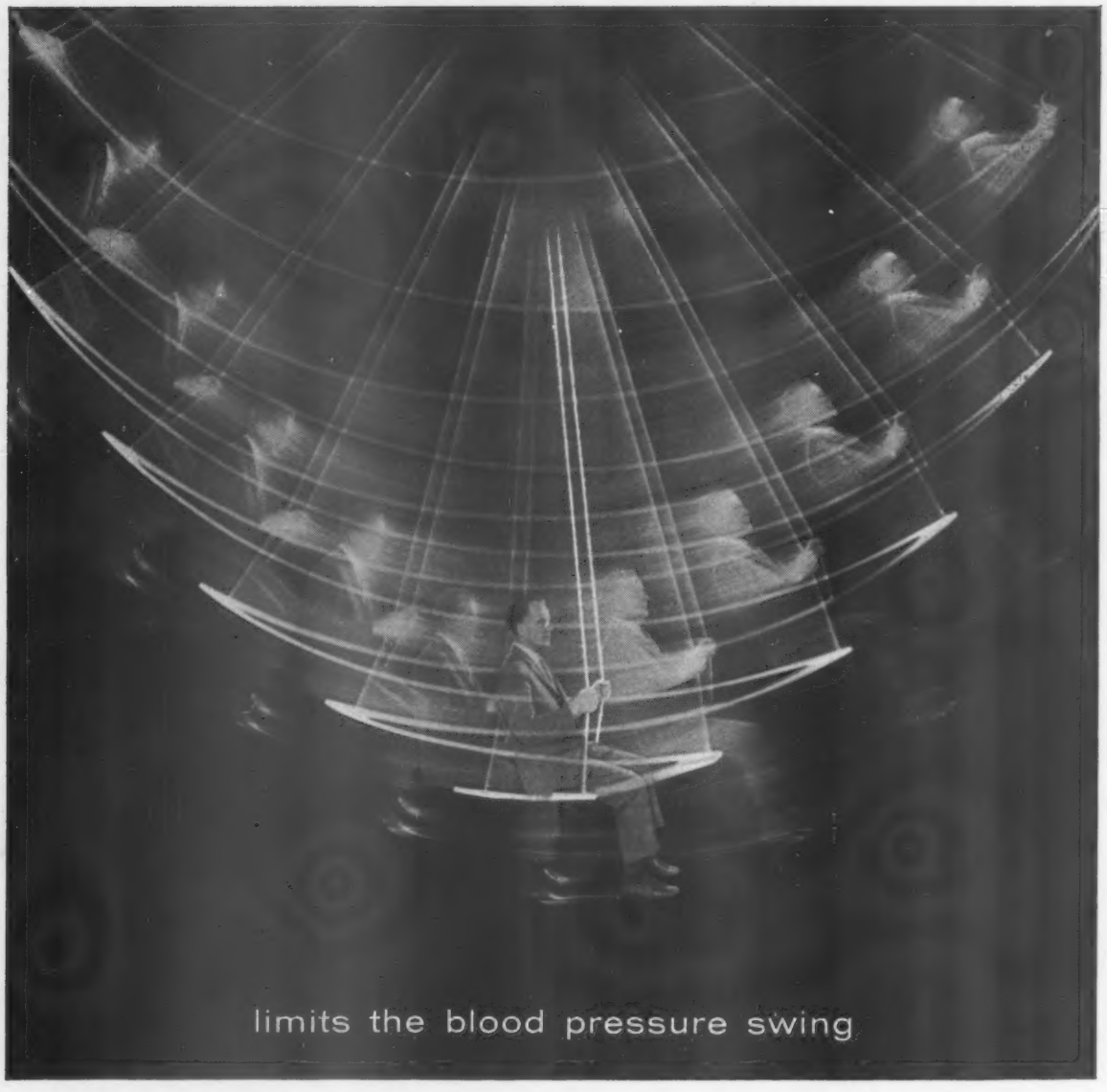
The American Journal of Cardiology

Volume VIII SEPTEMBER 1961 Number 3

CONTENTS

Clinical Studies

Contents continued on page 7



Rautrax-N lowers high blood pressure gently, gradually . . . protects against sharp fluctuations in the normal pressure swing.

Rautrax-N offers all the advantages of Raudixin, Naturetin and potassium chloride in a single dosage form *plus: increased efficacy* – Combined action of Raudixin and Naturetin results in a potentiated antihypertensive effect greater than that produced by either drug alone. *increased safety* – Potentiated action permits lower dose of other antihypertensive agents, thus reducing severity of side effects. Protection against possible potassium depletion. *flexibility* – Interchangeable with either Raudixin or Naturetin ĉ K. *economy* – Maintenance dosage of only 1 or 2 tablets daily for most patients. *convenience* – Once-a-day maintenance dosage. Two potencies available.

***Supply:* *Rautrax-N* – capsule-shaped tablets providing 50 mg. Raudixin, 4 mg. Naturetin and 400 mg. potassium chloride. *Rautrax-N Modified* – capsule-shaped tablets providing 50 mg. Raudixin, 2 mg. Naturetin and 400 mg. potassium chloride.**

Rautrax-N*

Squibb Standardized Whole Root Rauwolfia Serpentina (Raudixin) and Bendroflumethiazide (*Naturetin) with Potassium Chloride

For full information, see your Squibb Product Reference or Product Brief.

SQUIBB

Squibb Quality – the Priceless Ingredient

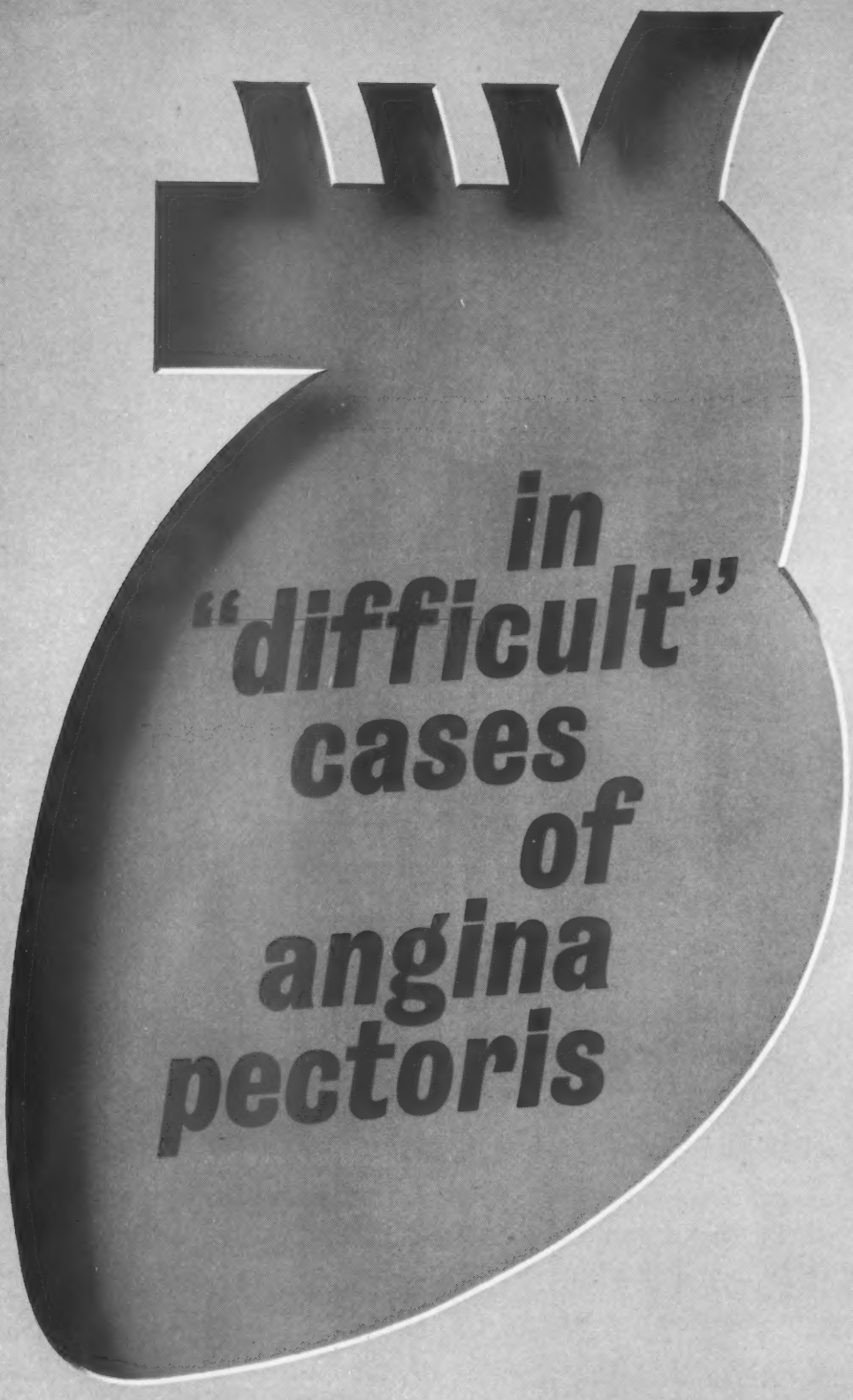
'RAUDIXIN'®, 'RAUTRAX'® AND 'NATURETIN'® ARE SQUIBB TRADEMARKS.

CONTENTS continued—September 1961

VOLUME EIGHT NUMBER THREE

Experimental Studies

Contents continued on page 9



Marplan

prevents anginal pain[1-4]
increases exercise tolerance[2,5,6]
reduces nitroglycerin requirements[2,3]

A potent regulator of amine oxidase, Marplan has demonstrated a high degree of effectiveness in moderately severe to intractable angina pectoris. Improvement on Marplan ranged from a reduction in the number of attacks to virtual abolition of the anginal state. With Marplan, anginal relief is enhanced by a more confident mental climate — improving the chances of success of the entire prophylactic regimen. However, since the precise manner in which Marplan improves the cardiac status is as yet undefined, it is imperative that patients be instructed to maintain the same restrictions of activity in force prior to Marplan therapy. Consult literature and dosage information, available on request, before prescribing.

References: 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. 2. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, **Virginia M. Month.**, 87:23, 1960. 4. T. Winsor and P. Zarco, **Angiology**, 11: (Part 2), 67, 1960. 5. G. C. Griffith, **Clin. Med.**, 6:1555, 1959. 6. G. C. Griffith, **Dis. Nerv. System**, 21 (Suppl.), 101, 1960.

MARPLAN® — 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine

ROCHE
ROCHE
LABORATORIES
Division of Hoffmann-La Roche Inc.

CONTENTS continued—September 1961

VOLUME EIGHT NUMBER THREE

New Method

Review

Case Reports

Contents continued on page 11

Clinically Proven

in more than 750 published clinical studies
and over six years of clinical use

Outstandingly Safe and Effective

for the tense and nervous patient

1 simple dosage schedule relieves anxiety dependably — without the unknown dangers of "new and different" drugs

2 does not produce ataxia, stimulate the appetite or alter sexual function

3 no cumulative effects in long-term therapy

4 does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis

5 does not muddle the mind or affect normal behavior

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; bottles of 50. Also as MEPROTABS®–400 mg. *unmarked*, coated tablets; and in *sustained-release* capsules as MEPROSPAN®-400 and MEPROSPAN®-200 (containing respectively 400 mg. and 200 mg. meprobamate).
®TRADE-MARK

Miltown®
meprobamate (Wallace)

WALLACE LABORATORIES / *Cranbury, N. J.*

CM-4731

CONTENTS continued—September 1961

VOLUME EIGHT NUMBER THREE

Contents continued on page 13

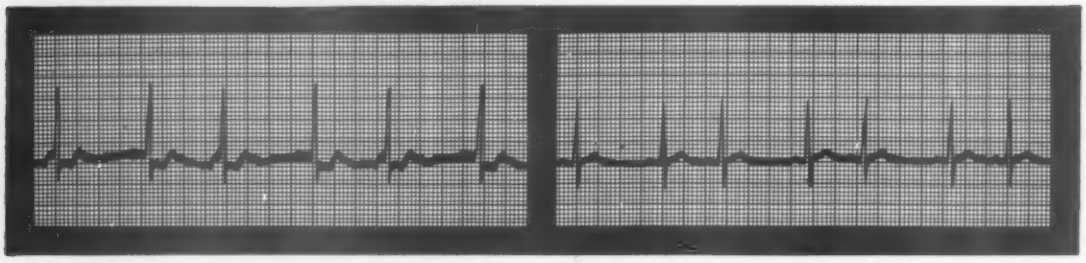
in coronary artery disease

with or without angina

Peritrate is basic for both

because it produces a substantial and sustained increase in myocardial blood flow...without significant change in cardiac output, blood pressure, or pulse rate

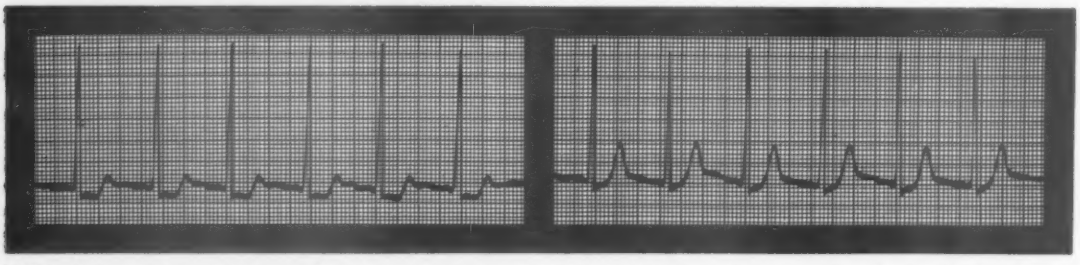
the patient with angina*



before **Peritrate**—S-T depression after standard exercise in anginal patient with no history of infarction.

after **Peritrate** (20 mg., administered 4 hours before exercise test). S-T segment near normal.

the postcoronary patient without angina*



before **Peritrate**—Abnormal ECG response to standard exercise in postinfarction patient without angina.

after **Peritrate** (20 mg., administered 90 minutes before exercise test). S-T segment near normal.

*Electrocardiograms and case histories on file in the Medical Department, Warner-Chilcott Laboratories.

Full dosage information, available on request, should be consulted before initiating therapy.

basic therapy in coronary artery disease
—with or without angina

Peritrate®

brand of pentaerythritol tetranitrate

Watch your mail for the ECG Interpretation Series

WARNER CHILCOTT

MORRIS PLAINS, N.J.

makers of Tedral Gelusil Proloid Mandelamine

GP 12 REV 1

CONTENTS continued—September 1961

VOLUME EIGHT NUMBER THREE

Diagnostic Shelf

Special Departments

1962 Annual Convention

AMERICAN COLLEGE OF CARDIOLOGY

The Eleventh Annual Convention of the College will be held in Denver, Colorado at the Denver Hilton, May 29 to June 2, 1962.

Abstracts of papers intended for the scientific program should be sent before January 1, 1962 to Dr. James E. Crockett, Department of Medicine, University of Kansas Medical Center, Kansas City, Kansas. Abstracts should be approximately 250 words in length. Original and three copies are to be supplied.

Commercial exhibitors should write to Dr. Philip Reichert, Executive Director of the College, Empire State Building, New York 1, New York. Journal advertisers will have point priority in the assignment of exhibit space.

Abstracts of scientific exhibits should also be sent to the office of the Executive Director.

Index to Advertisers on pages 63 and 64

A report of nutrition teaching in elementary textbooks

Leading educators believe that nutrition education should start in the early grades. A good three-quarters of both principals and teachers who think their students do not get three balanced meals *say breakfast is most apt to be neglected.** A recent study made by educational consultants found in 34 elementary health textbooks that among other breakfasts, a basic cereal breakfast appeared in the majority of textbooks examined. The majority of textbooks examined included breakfast teaching ideas based on the Iowa Breakfast Studies.** The Iowa Breakfast Study of School Boys demonstrated that students worked better and the majority of them had a definitely better attitude and a better scholastic record when a good breakfast was eaten.

**A Study of the Teaching of Nutrition in the Public Schools Published by Cereal Institute, Inc., January, 1952*

***A Summary of the Iowa Breakfast Studies Published by Cereal Institute, Inc., May, 1957*

CEREALS ARE LOW IN FAT

CEREAL INSTITUTE, INC.

135 South LaSalle Street, Chicago 3

A research and educational endeavor devoted to the betterment of national nutrition

now... Rx

Tindal®

acetophenazine dimaleate

new calming agent with mild sedative effect

Schering

■ helps the cardiac or hypertensive patient slow down to the safer pace you recommend ■ controls the agitation and tension that aggravate his condition[1,2] ■ calms the patient and helps him get to sleep more easily ■ relatively free of side effects[1-3] ■ low in cost, particularly when long-term or adjunctive therapy is indicated

dosage: Total daily dosage may range from as low as 40 mg. (one 20 mg. tablet twice daily) to as high as 80 mg. daily. **Generally, the most effective dosage is 20 mg. t.i.d.** In those patients who have difficulty sleeping, the last tablet should be taken one hour before retiring.

supply: TINDAL Tablets, 20 mg., bottles of 100 and 1000.

references: (1) Hirshleifer, L.: Adjunctive therapy in cardiacs, presented at the Spring Scientific Symposium, Connecticut Acad. Gen. Pract., Hartford, Conn., March 16, 1961. (2) Fronman, I. P.: The Alleviation of Stress in the Elderly Cardiac Patient, **ibid.** (3) Kent, E. A.: Management of the Hyperactive Geriatric Patient, **ibid.**

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

5-811

FOR YOUR CARDIOVASCULAR PATIENT...WHEN YOU HAVE TO SAY

SLOW DOWN

Where blood pressure climbs —keep it under control with Enduronyl

Announcing a once-a-day thiazide/rauwolfia antihypertensive

ENDURONYL

Trademark

(Methyclothiazide and Deserpidine, Abbott) (ENDURON™ and HARMONYL®)

Yes, just *once* daily is the dose for hypertension. Blood pressure starts down steadily: improvement usually is substantial within 10 days. Further reduction may continue over following weeks. At the same time, excess sodium and water are consistently eliminated.

Giving Enduronyl just once a day means fewer forgotten doses. A smoothly sustained therapeutic response, too.

On the other hand, single doses produce only one low, brief peak of potassium excretion. Hence one-a-day dosage means reduced chance of potassium depletion, since there's but one daily boost to the patient's potassium outgo.

WHAT IS ENDURONYL?

Enduronyl combines two well-established antihypertensive agents: (1) Enduron, Abbott's long-acting thiazide diuretic, and (2) Harmonyl, a rauwolfia derivative of low side effects. Together they provide greater hypotensive action than with either alone.

Enduronyl is supplied in two formulas, to cover a wide range of cases from mild to moderately severe hypertension. Would you like the literature? Write Abbott, North Chicago, Ill.

Supplied:
Enduronyl—(5 mg. Enduron, and 0.25 mg. Harmonyl)
Enduronyl Forte—(5 mg. Enduron, and 0.5 mg. Harmonyl)

ABBOTT

109225

MORE SECURITY IN POSTCORONARY YEARS

DANILONE®

(Phenindione, Schieffelin)

A "MAXIMUM SECURITY" ANTICOAGULANT

FAST, PRECISE ADJUSTMENT OF PROTHROMBIN LEVEL

After recovery from a myocardial infarction, DANILONE—a "maximum security" anticoagulant—guards the patient against the inevitable[1] subsequent recurrence with less risk of hemorrhage. **DANILONE has a short latent period and a short recovery period, and therefore, noncumulative action.** Thus, the prothrombin level may be rapidly and accurately adjusted upward or downward by simple alteration of oral dosage. DANILONE may be administered to many patients with shock, debilitation, hepatic, renal or gastrointestinal disease. The practical advantages of DANILONE are well documented.

EARLY ONSET "...fast in reaching therapeutic levels..."[2]

FAST DISSIPATION "...rapid return to a normal level in the event of undue prolongation of prothrombin time or hemorrhage."[3] (After withdrawal of DANILONE, the return to normal range of prothrombin time is well advanced in 24 hours, complete in 40 hours.)

RECORD OF SAFETY "...can be administered with reasonable safety in the presence of many conditions (other than that for which the anticoagulant is administered)..."[4]

The short latent period and rapid return to normal prothrombin blood levels when DANILONE is discontinued allow the physician to obtain even more satisfactory control by dividing the daily dose into two twelve-hour intervals.

"An advantage of a twelve-hour dosage schedule is that only half the daily dose may have been given when bleeding or excess prothrombin effect is discovered, allowing earlier adjustment of dosage or discontinuance."[4]

FEWER PROTHROMBIN DETERMINATIONS REQUIRED "...patients on long-term therapy can usually be...controlled with estimations at two- to four-week intervals,"[5] after initial adjustment period.

ECONOMICAL "...We have found phenindione inexpensive..."[3]

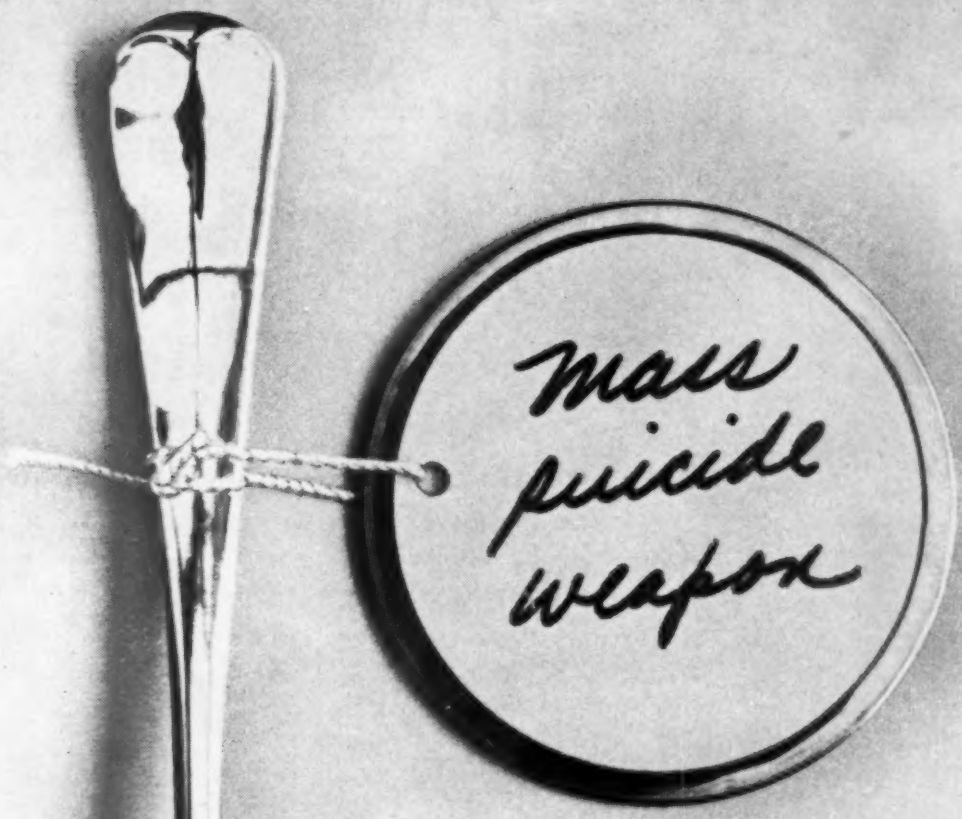
PREDICTABLE "...and relatively easy to manage with a reasonably constant daily dosage."[3]

Complete literature available on request to physicians for indications, dosages and precautions.

Supplied: In 50 mg. scored tablets, bottles of 100 and 1,000.

1. Manchester, B.: Ann. Int. Med. *47*:1202 (Dec.) 1957. 2. Harper, B.F., and Johnson, R.: J.M.A. Georgia *45*:149 (April) 1956. 3. Wood, J.L. *et al.*: J.A.M.A. *159*:635 (Oct.) 1955. 4. Sise, H. *et al.*: Am. Heart J. *53*:132 (Jan.) 1957. 5. Dewar, H.A.: Practitioner *186*:41 (Jan.) 1961.

Schieffelin & Co. / Since 1794 Schieffelin Pharmaceutical Laboratories Division, New York 3, N. Y.



Overeating takes many Americans to an early grave
according to a massive, four-year study of five million insured Americans.*

Overeating can be avoided with Tepanil—
curbs appetite without appreciable CNS, vasopressor or psychic stimulation.

---

even in the presence of hypertension, diabetes, or heart disease ▪ **even** during and after pregnancy ▪ **even** when patients no longer lose weight on other drugs ▪ **even** in adolescents ▪ **even** in the evening

for continuous appetite control

NEW

Tepanil® Ten-tab

(DIETHYLPROPION 'NATIONAL' CONTINUOUS RELEASE FORM)

one tablet at 10 A.M. curbs appetite all day!

Also available: TEPANIL® Regular Tablets, when divided dosage is desired. One tablet **t.i.d.**, one hour before meals and at 8 P.M. to curb midnight snacks.

Side Effects: Clinically, side effects are rare. Approximately 3 per cent of the patients report dryness of the mouth or thirst. Supplied: **Tepanil Ten-tab** — Continuous Release Tablets of 75 mg. Bottles of 30. **Tepanil** — Tablets of 25 mg. Bottles of 100 and 1000.

*Build and Blood Pressure Study, Society of Actuaries, Chicago, Ill., 1959, vol. 1, pp. 84, 89, 92.

Trademark: TEN-TAB T-3479/60-1

Division of Richardson-Merrell Inc.
THE NATIONAL DRUG COMPANY
Philadelphia 44, Pa.

acts directly on peripheral arterial walls . . . produces gradual, sustained vasodilatation without disturbing hemodynamics

CYCLOSPASMOL*

CYCLANDELATE

in peripheral vascular disease

Cyclospasmol is more effective in the treatment of arteriosclerosis obliterans and for the relief of intermittent claudication than sympatholytic and adrenergic blocking agents, because it acts directly on the arterial musculature.

- does not produce tachycardia, syncope or hypotension—may be used with safety in most patients having cerebral and coronary vascular diseases.
- dilates the deeper arteries as well as the superficial vessels to improve blood flow to the extremities.
- orally effective; produces a gradually increasing vasodilatation—aids in the healing of trophic leg ulcers.

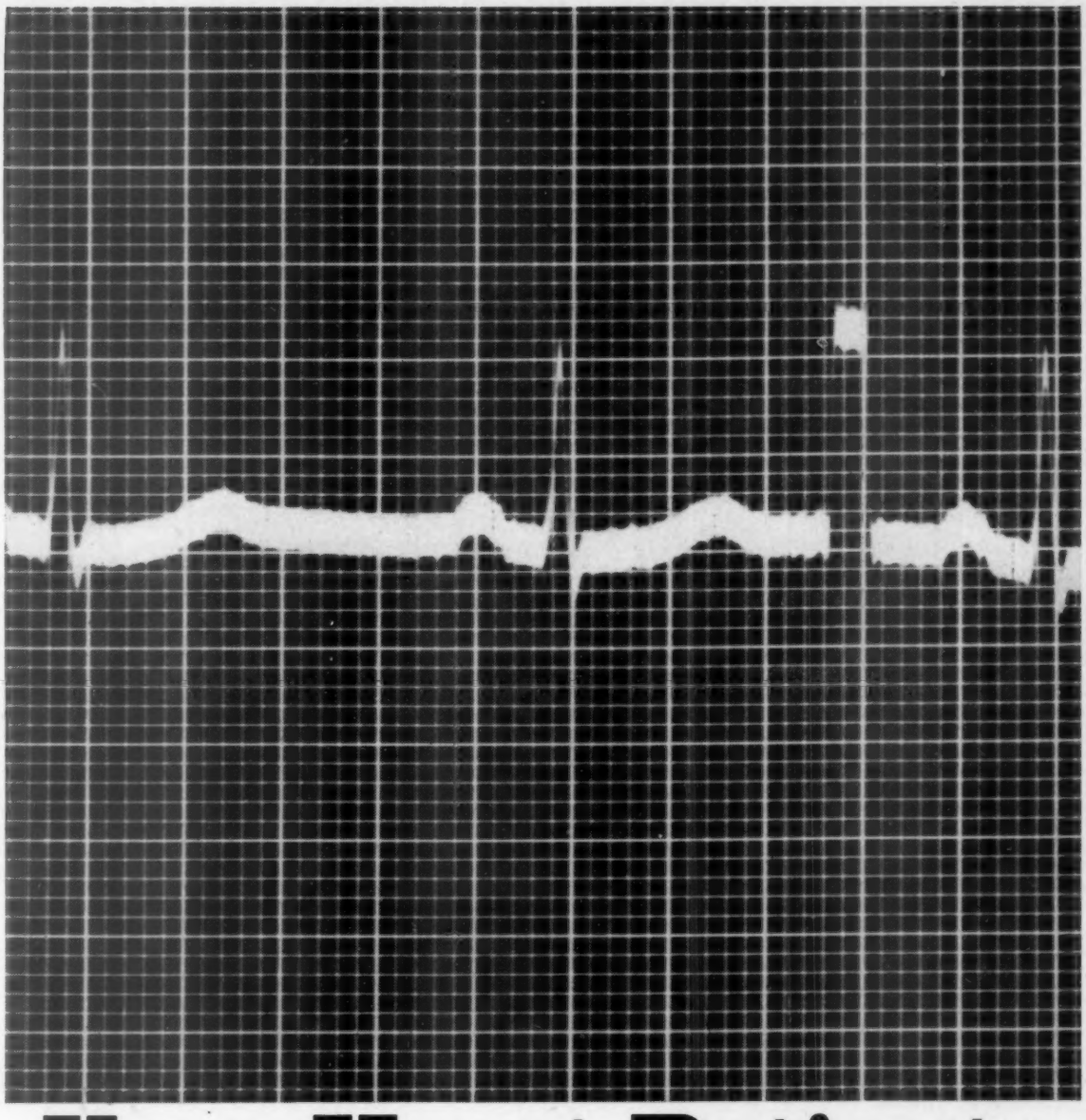
Dosage: Usual dosage is two tablets (200 mg.) four times daily. Dosage range is from one to three tablets, q.i.d. Continued therapy and *individualized* dosage, depending upon response, is necessary for maximum effectiveness. Supply: 100 mg. tablets, bottles of 100.

References: 1. Council on Drugs, New and Nonofficial Drugs, J.A.M.A. *170*:1670; 1959. 2. Leslie, Robert E.: Effects of Cyclandelate (Cyclospasmol®) In Treatment of Circulatory Disturbances, Tex. J. Med. *56*:352-356, 1960. 3. Popkin, R. J.: Combined Vasodilator Therapy in Peripheral Vascular Diseases, J. Am. Geriatrics Soc. VIII: 638-643, 1960. 4. Van Wijk, T. W.: Angiology *4*:103, 1953. 5. Gillhespy, R. O.: Brit. M. J. *2*:1543, 1957. 6. Gillhespy, R. O.: Angiology *7*:27, 1956.

Professional literature and samples available on request

IVES IVES-CAMERON COMPANY
New York 16, N. Y.

*Trademark



Your Heart Patient

– and a natural way to meet his need for milk's nutrition
– without risking the penalties of fat

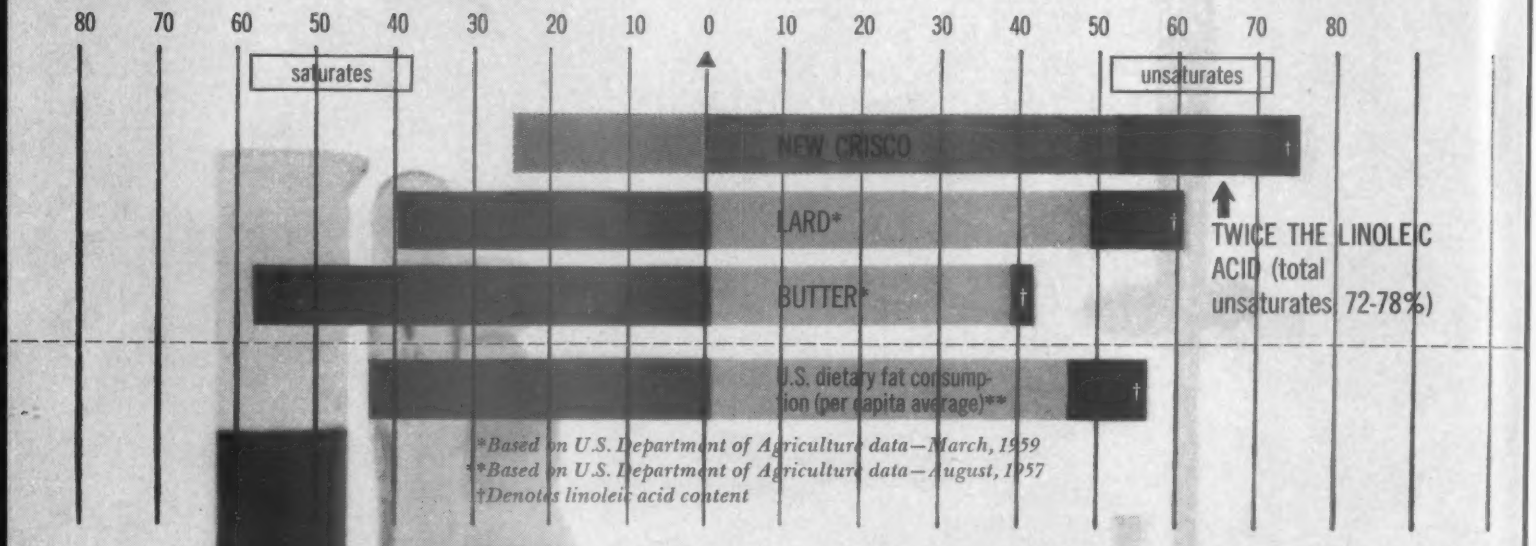
Although your heart patients need the vital nutrition of milk, often the calories and saturated fat both pose problems.

Now there's a fresh-flavor, delicious, and *natural* way to help assure your patients' good nutritional status. Today, Carnation Instant Nonfat Dry Milk provides all the protein, calcium, and B-vitamins of fresh, whole milk — but without the fat.

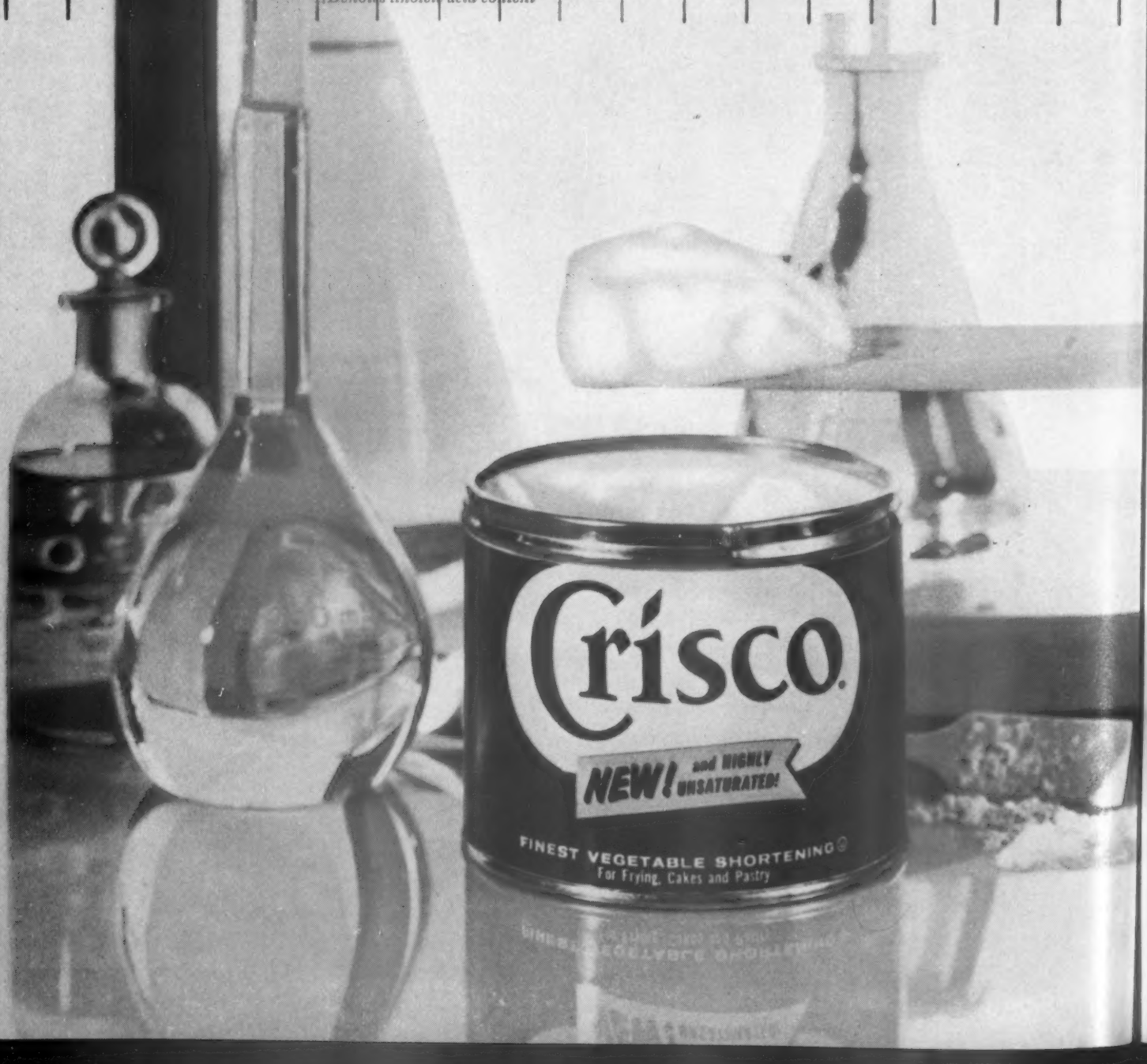
And Carnation Instant can be mixed 25% over-strength to provide more calcium, protein, and B-vitamins than ordinary nonfat milk. ⅓ cup extra crystals per liquid quart gives patients 25% more needed nutrition—*without* excessive calories. It tastes delicious, with a richer flavor they'll enjoy. Even enriched, it costs them only 12¢ a quart.

ANOTHER QUALITY PRODUCT OF CARNATION COMPANY, LOS ANGELES 36, CALIFORNIA

Compare
NEW CRISCO'S improved level of preferred lipid factors



**Based on U.S. Department of Agriculture data—March, 1959*
***Based on U.S. Department of Agriculture data—August, 1957*
†Denotes linoleic acid content



Your wife can tell you why real shortening is needed for good cooking...

NEW CRISCO®

THE HIGHLY UNSATURATED SHORTENING

doubles the linoleic acid to answer the need for an all-purpose shortening in line with changing views on dietary fat

You, as a physician, know the desirability of adequate sources of linoleic acid even in normal diets. Your wife knows how important shortening is in preparing fine-tasting foods.

Today's prudent diets dictate a more balanced intake of preferred unsaturates—even though a direct causal relationship between dietary fats, serum lipid levels, and cardiovascular diseases is not yet proved.

Helps you prescribe diets patients will follow!

Your patients know the desirability of *real* shortening for all frying and baking because of the wonderful eating characteristics it alone gives to many foods. In fact many of our favorite foods, for example most cakes, cookies, and pastry, can *only* be satisfactorily made with a real shortening, not salad oil. And you know how difficult it is to give up favorite foods—even on doctor's orders.

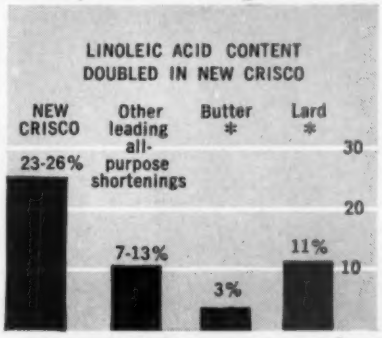
The importance of new Crisco

Hence the importance to you and your patients of new, improved Crisco: A highly unsaturated *vegetable* shortening, new Crisco now provides approximately double the linoleic acid (23-26 per cent) of other leading all-purpose shortenings—and a total of 72-78 per cent unsaturates. In one-half cup of new Crisco there are actually 22 grams of linoleic acid.

For you, this technical achievement means relief from worry about shortenings when patients ask your advice about what are the preferred fats to use. For these patients, use of highly unsaturated new Crisco will permit enjoyment of the advantages of the finest vegetable shortening—yet it also permits them to be on the preferred side dietetically.

Can be recommended with confidence

New Crisco achieves a more favorable level of preferred unsaturates in line with current fat concepts and can be recommended with confidence. Crisco's outstanding *digestibility, performance, appearance,* and *all-purpose versatility* are unchanged.



NEW CRISCO Fatty Acid Composition (Grams/100 Grams)	
Total Unsaturates	72-78
Polyunsaturates. Linoleic	23-26
Others	4-5
Mono-unsaturates	44-50
Total Saturates	22-28
Natural Tocopherols	0.1
Cholesterol	None
Salt (Sodium Chloride)	None

As a highly unsaturated vegetable shortening, with double the linoleic acid content, new Crisco is designed to satisfy not only the needs of the good cook but also the new requirements of the nutrition scientist and physician. CD261

PROCTER & GAMBLE • CINCINNATI, OHIO

HY-0984

Hygroton®

brand of chlorthalidone

in hypertension and edema

17 days free each month from drug administration

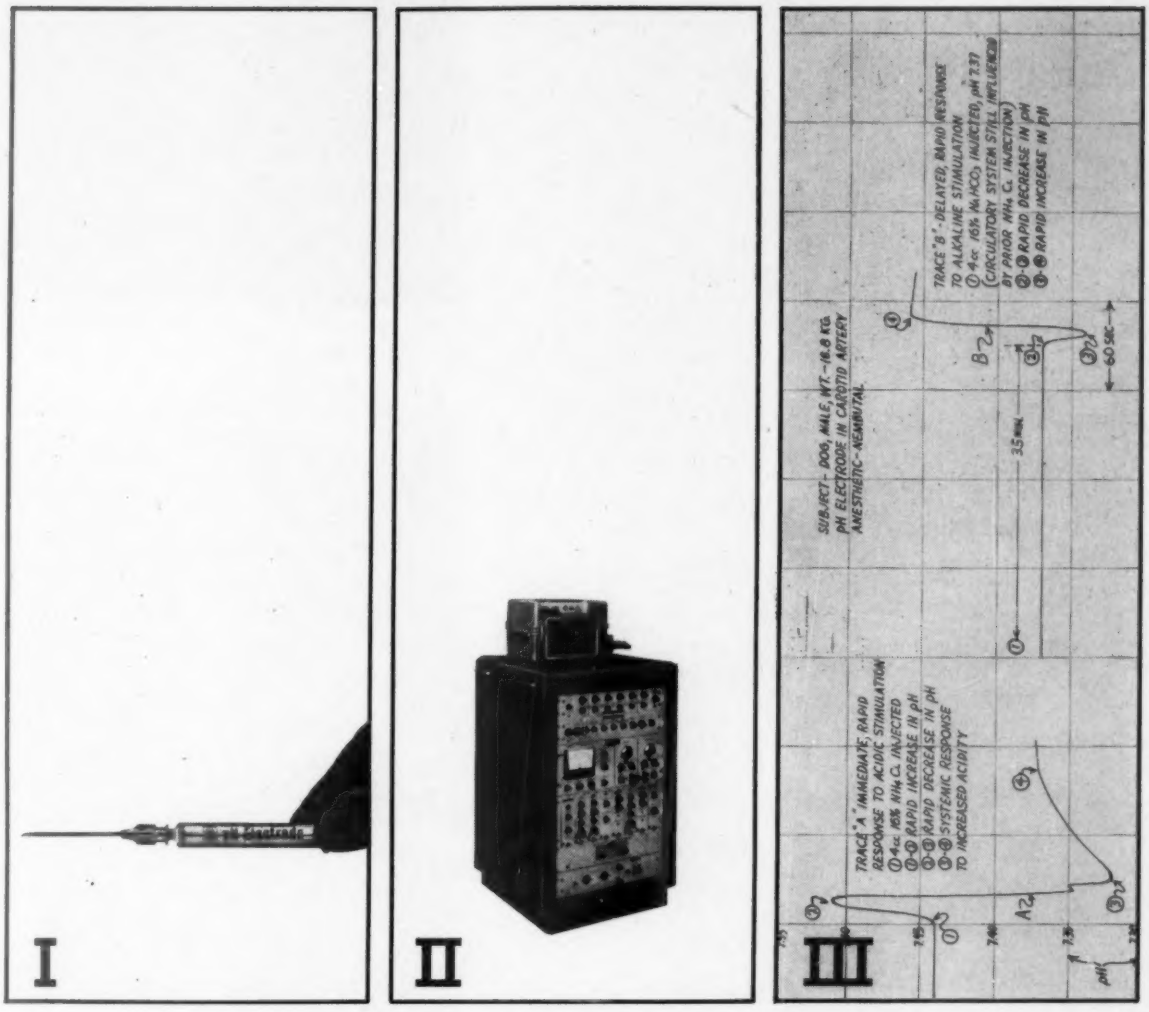
just one tablet Mon. Wed. Fri.

The longest-acting by far of all the new agents introduced for hypertension and edema, Hygroton provides a smoother, less abrupt action which is sustained for as long as 72 hours...can initiate and maintain therapy on just 3 doses a week... saves the patient over ⅓ in cost without sacrifice of therapeutic benefit.

Hygroton® Tablets, 100 mg., bottles of 100.

Geigy

Geigy Pharmaceuticals
Division of
Geigy Chemical Corporation
Ardsley, New York



HONEYWELL MEASURES *in vivo* pH PLUS

Now being used in bio-medical research, the *in vivo* pH channel is one of the twenty-eight physiological measurement channels which you may select for your Honeywell Electronic Medical System.

The new Honeywell pH electrode enables you to now measure and record blood pH continuously with consistent accuracy. A one-piece instrument in which both active and reference electrodes are within a hypodermic needle, its accompanying circuitry is permanently sealed within the syringe barrel. The electrode (I) and its amplifier make up only one channel of a typical Honeywell Electronic Medical System (II).

The pH record (III) is produced immediately (and simultaneously with contemporary data) on a direct-writing Honeywell multi-channel Visicorder oscillograph. Other Honeywell recorders, digital print-out devices, tape recorders, and automatic data reduction equipment are available for incorporation into any Honeywell Electronic Medical System.

MINNEAPOLIS-HONEYWELL ELECTRONIC MEDICAL SYSTEMS
5202 EAST EVANS AVENUE · DENVER 22, COLORADO

Honeywell

Electronic Medical Systems

pH study courtesy T. W. Nielsen, Ph.D., Department of Physiology, University of Colorado Medical School

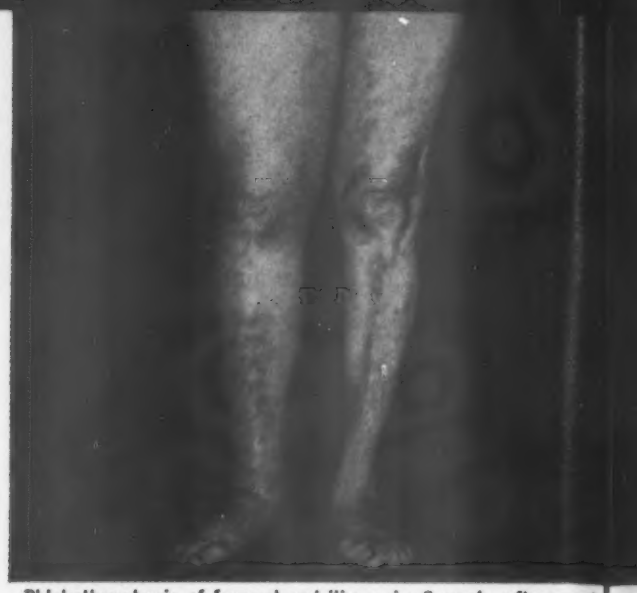
BEFORE

LYOVAC®

THROMBOLYSIN®

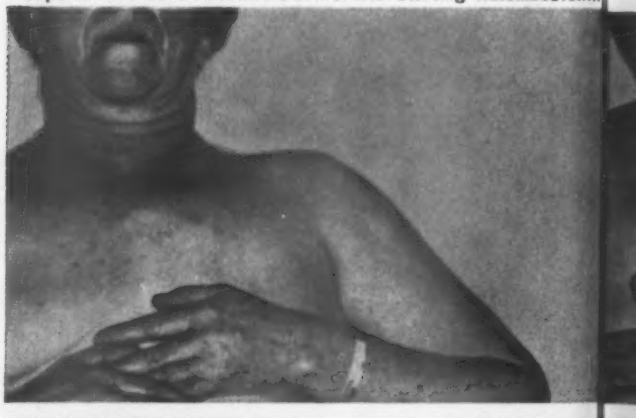
FIBRINOLYSIN (HUMAN)

a new agent
for lysis of
vascular thrombi



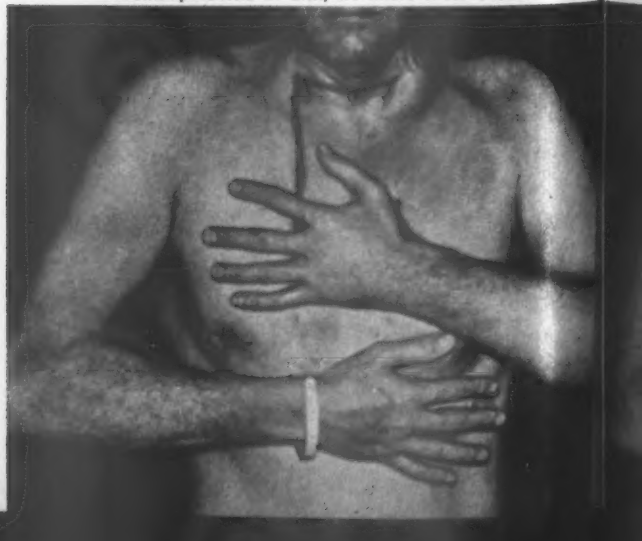
Phlebothrombosis of femoral and iliac vein, 3 weeks after onset.

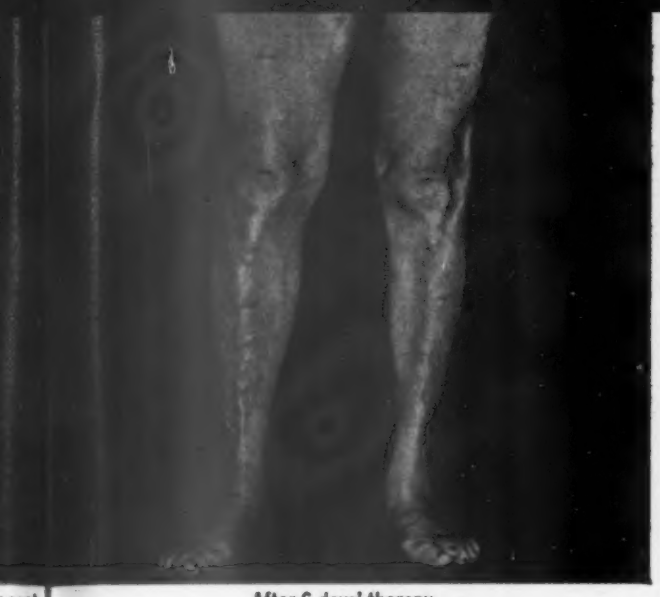
Superior vena cava thrombosis (8 hrs. after starting THROMBOLYSIN).



Phlebothrombosis (8 weeks' duration in left leg, 6 weeks' in right).

Thrombophlebitis of arm, 24 hours after onset.



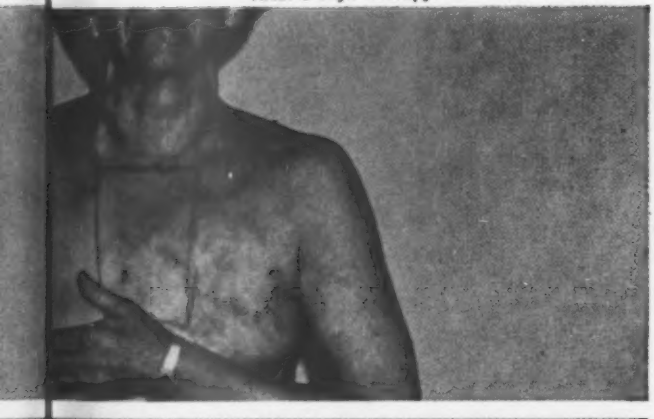


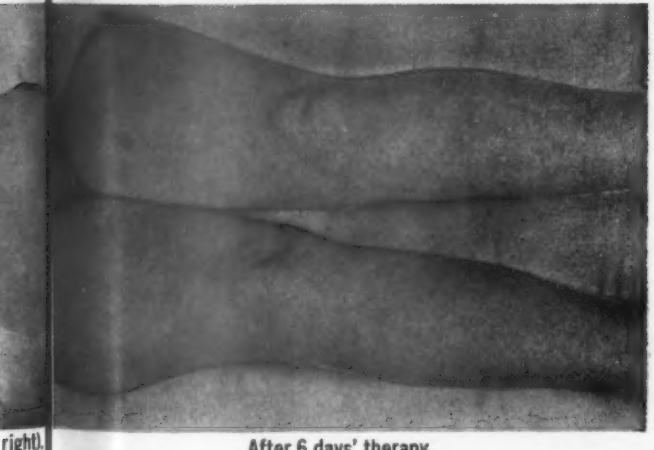
onset.

After 6 days' therapy.

LYSIN).

After 3 days' therapy.

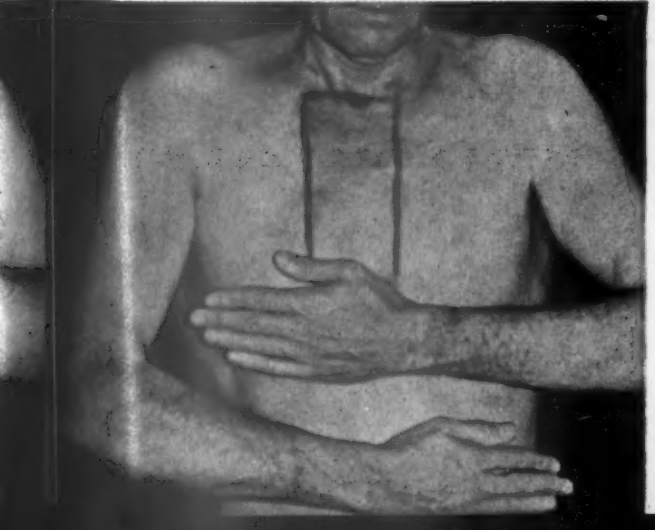




right).

After 6 days' therapy.

After 5 days' therapy.



AFTER

LYOVAC®

THROMBOLYSIN®

FIBRINOLYSIN (HUMAN)

in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi*, LYOVAC® THROMBOLYSIN makes possible

- lysis of formed clots
- reduced mortality and morbidity, shortened hospitalization
- reduced incidence of postphlebitic complications

with decreased incidence of reactions such as fever, chills, or malaise of severe proportions; higher degree of safety; greater, more predictable potency.

Supply: Each bottle contains 50,000 MSD units.

*See package circular for qualifications concerning cerebrovascular accidents and myocardial infarction.

Before prescribing or administering THROMBOLYSIN, *the physician should consult the detailed information on use accompanying the package or available on request.*

MSD

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC., WEST POINT, PA.

CAPLA™

(mebutamate, Wallace)
CENTRAL ACTING PRESSURE LOWERING AGENT

ANNOUNCING

CAPLA™

A new drug that works in a new way to control blood pressure without serious side effects

CAPLA™

(mebutamate, Wallace)
CENTRAL ACTING PRESSURE LOWERING AGENT

Capla acts centrally at the brainstem vasomotor center

Reduces blood pressure by central action
is not a ganglionic blocker

Capla is a new *kind* of drug to treat hypertension. Chemically, Capla is 2-methyl-2-*sec*-butyl-1, 3-propanediol dicarbamate. It is unrelated chemically to any other antihypertensive agent. Capla does not block ganglia, reduce blood volume or interfere with neurohormonal balance.

New therapy for hypertension

Because of its action at the brainstem vasomotor control center, Capla is a new therapy for hypertension. It is effective alone in the treatment of mild to moderate hypertension, and can be combined with diuretics or peripherally acting antihypertensives in more severe cases.

Exceptionally well tolerated

Capla acts rapidly, producing substantial blood pressure reduction within two hours, yet it does not produce postural hypotension. It has proved exceptionally well tolerated in clinical use and has no known contraindications. Capla has not produced changes in renal, hematological, hepatic or endocrine function. It is rapidly eliminated and has no cumulative effects.

CAPLA™

(*mebutamate, Wallace*)
CENTRAL ACTING PRESSURE LOWERING AGENT

Controls blood pressure without serious side effects

Capla does not produce depression, postural hypotension, nasal congestion or gastric hyperacidity

Capla helps minimize one of the most difficult problems of hypertension therapy – unwanted and often serious side effects.

With Capla you have effective therapy without the unpleasant side effects which often cause patients to abandon treatment.

Side effects with Capla, when they do occur, are mild and usually transient. Transient drowsiness sometimes occurs, usually at higher dosage.

Mild calming effect

Patients on Capla often report a mild calming effect. This effect, together with the unusual freedom from serious side effects, makes therapy gratifying for both the patient and the physician.

Compatible with other drugs

Hypertensive patients with other disorders can receive Capla along with other medications.

For example, patients with congestive heart failure, angina, and diabetes mellitus can receive Capla along with such medications as digitalis, nitrates, and insulin—without aggravating these other disorders.

CAPLA™

(mebutamate, Wallace)

CENTRAL ACTING PRESSURE LOWERING AGENT

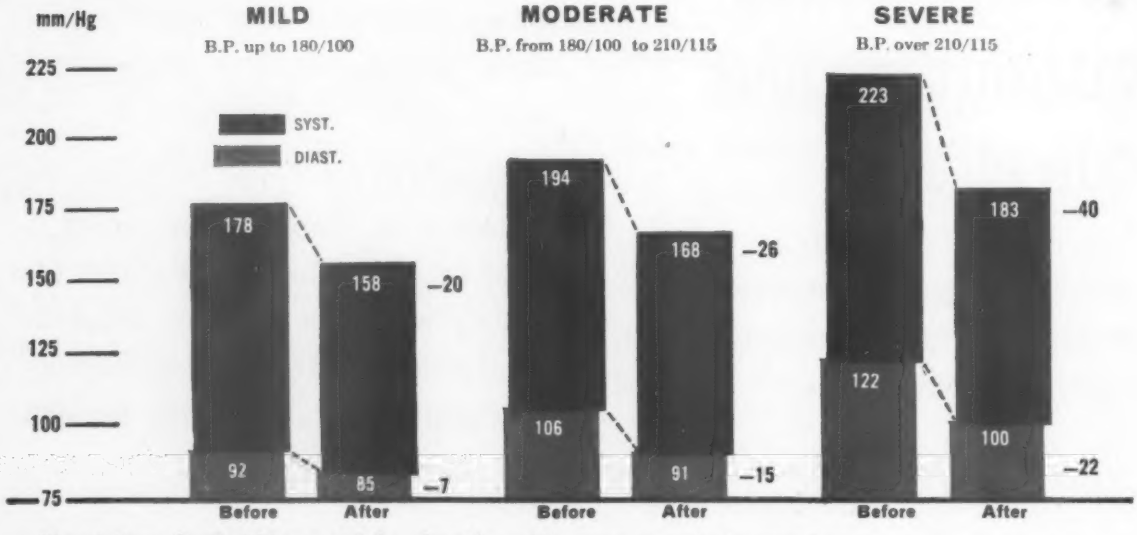
Lowers blood pressure effectively in clinical use

CLINICAL & PHARMACOLOGICAL REPORTS

1. Berger, F. M., and Margolin, S.: A Centrally Acting Blood Pressure Lowering Agent (W-583). Fed. Proc. 20:113 (March) 1961. 2. Diamond, S., and Schwartz, M. Scientific Exhibit at Ill. State Med. Soc. Chicago, (May) 1961. 3. Douglas, J. F., Ludwig, B. J., Ginsberg, T. and Berger, F. M.: Studies on W-583 Metabolism. Fed. Proc. 20:113 (March) 1961. 4. Duarte, C., Brest, A. N., Kodama, R., Naso, F., and Moyer, J. H.: Observations on the Antihypertensive Effectiveness of a New Propanediol Dicarbamate (W-583). Curr. Ther. Res., 2:148-52 (May) 1960. 5. DuChez, J. W., Scientific Exhibit at Amer. Academy of Gen. Practice, Miami, (April) 1961. 6. Kletzkin, M., and Berger, F. M.: A Centrally Acting Antipressor agent. Fed. Proc. 20:113 (March) 1961. 7. Mulinos, M. G., Scientific Exhibit at Amer. Coll. Card. New York, (May) 1961. 8. Mulinos, M. G., Saltefors, S., Boyd, L. J. and Cronk, G. A.: Human Pharmacology Studies with W-583. Fed. Proc. 20:113 (March) 1961. 9. Shubin, H., Scientific Exhibit, Amer. Coll. Card. New York, (May) 1961.

Average Reductions In Systolic And Diastolic Blood Pressure Reported With Capla

(325 patients)



Usual dose, Capla 300 mg., q.i.d.—duration of therapy, 3 weeks to over 1 year.

These data show that Capla reduces both systolic and diastolic blood pressure, usually in proportion to initial pre-treatment elevations.

CAPLA™

CENTRAL ACTING PRESSURE LOWERING AGENT

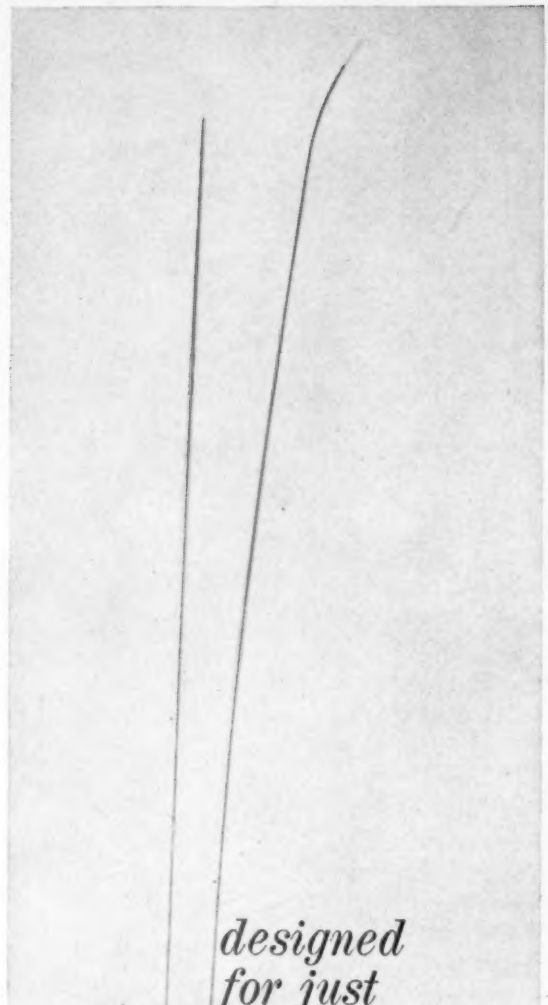
Wallace Laboratories
Cranbury, New Jersey

DOSAGE: the recommended dose of Capla is one 300 mg. tablet three or four times daily, before meals and at bedtime. The dosage should be adjusted to individual requirements; for example, older patients may require lower dosage.

COMPOSITION: each white, scored tablet contains 300 mg. of Capla (mebutamate, Wallace).

SUPPLIED: bottles of 100, scored tablets.

Literature and samples to physicians on request.



A measure of man's progress...

...has always been the specificity of his tools. Just as crude stone axes represented progress in primitive times, electronic calculators reflect the intellectual advancement of modern man. In recent years, however, scientific investigation has been so fruitful that specialized devices often could not keep pace. This "instrument lag," for example, has been noted in cardiovascular medicine.

In recognition of recent scientific advances and the pressing need for special instrumentation, Becton, Dickinson and Company has originated a CARDIOVASCULAR AND SPECIAL INSTRUMENTS SERVICE ***whose chief function is to make new instruments rapidly available for this vitally important area of medicine.***

Special research and development facilities have been created. A team of Becton-Dickinson specialists is devoting its full attention to the development of unique and experimental devices. But we believe today, as in the past, that it is you—the man behind the instrument—who knows best what changes or innovations are needed. Because this service can work only through a full, continuous partnership, we hope you will comment and make suggestions.

B-D would like to send you an illustrated catalog describing various products available for radiology, cardiovascular work, and cardiac surgery. Simply complete and mail coupon.

Becton, Dickinson and Company
Cardiovascular and Special Instruments Service
Dept. A-9
Rutherford, New Jersey

Please send me your Cardiovascular Product Catalog.

NAME_____, M.D.

ADDRESS_____

CITY_____ ZONE____ STATE_____

csi–CARDIOVASCULAR AND SPECIAL INSTRUMENTS SERVICE

B-D BECTON, DICKINSON AND COMPANY
RUTHERFORD, NEW JERSEY

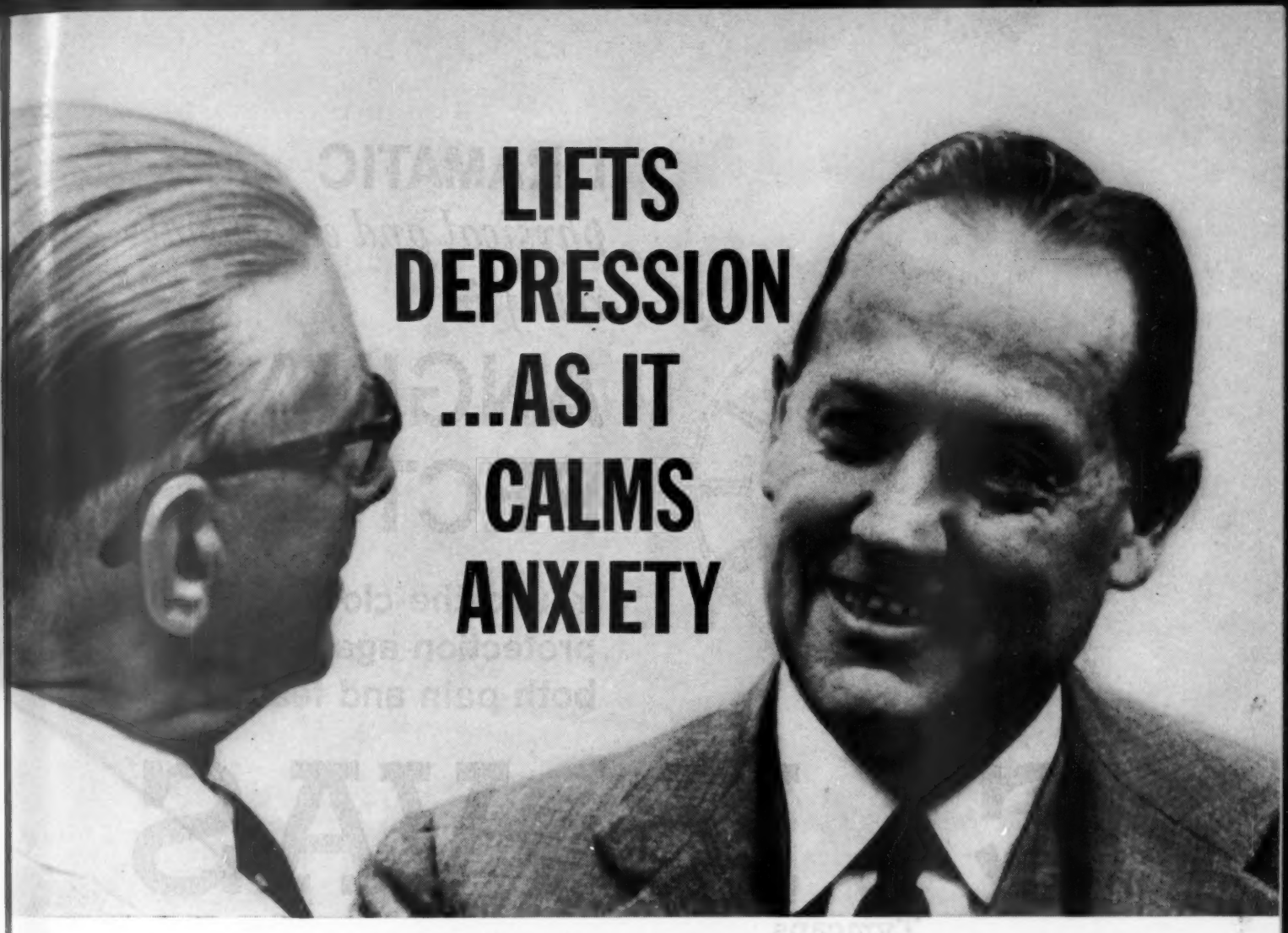
*Brockenbrough needle for transseptal left heart catheterization —18 gauge (regular wall), 71 cm. long.

86761

Sometime this month the 100,000,000th injection of Mercuhydrin will be given. We can interpret this figure in many ways . . . First of all, in terms of lives prolonged or saved . . . in terms of therapeutic advances, for the modern approach to therapy of congestive heart failure owes much to the long-established efficacy and safety of this drug. The published literature, clinical and experimental, is enormous and continuous. After more than 15 years Mercuhydrin remains the pharmacologic standard for the clinical comparison of diuretics. And as a pharmaceutical preparation, Mercuhydrin has not been surpassed in its stability and reliability. Lakeside is indeed proud of Mercuhydrin.

Lakeside Laboratories, Inc.

MERCUHYDRIN®, brand of meralluride sodium, Lakeside. **Supplied in 1 cc. and 2 cc. ampuls in boxes of 12, 25 and 100, and 10 cc. rubber capped, multiple dose vials in boxes of 6, 25 and 100. Needs no refrigeration. *Contraindications:* Acute nephritis and intractable oliguric states.**



Thanks to your balanced Deprol therapy... his depression has lifted and his mood has brightened up – while his anxiety and tension have been calmed down. He sleeps better, eats properly, and normal drive and interest have replaced his emotional fatigue.

Brightens up the mood, brings down tension

Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines. While energizers and amphetamines may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression and emotional fatigue.*

These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety – a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

Acts rapidly – you see improvement in a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – *often within a few days.* Thus, the expense to the patient of long-term drug therapy can be avoided.

Compatible with therapy for physical diseases. Deprol can be used safely with specific therapies for cardiovascular, G.I. and upper respiratory conditions. It does not cause liver toxicity, hypotension or tachycardia.

Deprol®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

WALLACE LABORATORIES / *Cranbury, N. J.*

CD-4489

DRAMATIC
physical and emotional relief in
ANGINA PECTORIS

'round-the-clock protection against both pain and fear

COROVAS

Tymcaps

COROVAS is a nontoxic, uniform-acting, long-acting vasodilator to control or prevent attacks of angina pectoris. One COROVAS Tymcap upon arising provides up to 12 hours of continuous coronary vasodilation, and another COROVAS Tymcap before the evening meal affords maximum protection against seizures all night. COROVAS alleviates the associated fear of pain. Reduces the need for emergency nitroglycerin. Safe and effective for long-term therapy.

SUPPLIED—Boxes of 60 and 120.

PROLONGED, SUSTAINED ACTION OF VASODILATING PENTAERYTHRITOL TETRANITRATE (PETN) 30 MG., AND SEDATIVE SECOBARBITURIC ACID 50 MG. IN EACH COROVAS TYMCAP.
As with all nitrates, use with caution in glaucoma.

AMFRE GRANT, INC.
Brooklyn 26, N. Y.

NEW!

AO CARDIOMETER®

Developed in cooperation with Dr. K. William Edmark, Surgeon, Seattle, Washington

. . . the complete Cardiac Monitor and Control Instrument for your Patients!

The New AO Cardiometer combines four instruments within a single, compact unit: Cardiotachometer, Cardioscope, Automatic Pacemaker and Continuous Internal-External Pacemaker. This practical combination of functions gives the surgeon, anesthesiologist or clinician the most complete visual and audible cardiac control of the patient, plus the necessary expedient automatic resuscitative action at the moment of cardiac arrest.

Here are some of the many outstanding features offered by this exceptional instrument:

Direct Heart-Rate Readout in beats per minute is registered on large easy-to-see dial.

Dual Alarm System can be preset to sound at minimum (asystole) and maximum (tachycardia, flutter, fibrillation) tolerances.

EKG on Built-In Oscilloscope allows continuous observation of the QRS Complex . . . gives simultaneous display of pace signal when patient is under pacemaker control.

The AO Cardiometer is a proved instrument, used for constant cardiac monitoring in more than 400 cases of major thoracic and abdominal surgery. You will find this instrument to be worthy of your utmost confidence. Why not arrange for a demonstration of the AO Cardiometer as soon as possible?

American Optical
COMPANY
INSTRUMENT DIVISION, BUFFALO 15, NEW YORK

Dept. W293
Gentlemen:
Please arrange demonstration of AO Cardiometer.
Name.....
Address.....
City.....Zone.....State.....

IN CANADA write — American Optical Company Canada Ltd., Box 40, Terminal A, Toronto, Ontario

CAMBRIDGE "Versa-Scribe" ELECTROCARDIOGRAPH

CAMBRIDGE
VERSA-SCRIBE
Electrocardiograph
Model VSM (mobile).

WITH SPECIALLY DESIGNED CARRIAGE FOR MOBILE USE

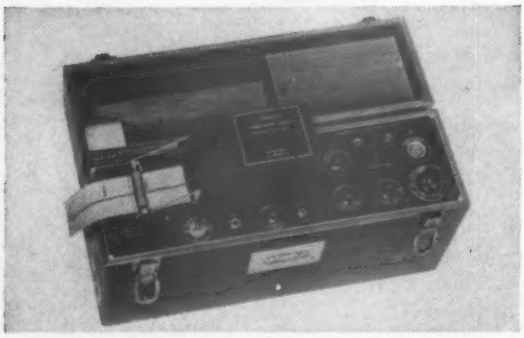
The "Versa-Scribe" fits snugly into a container which is an integral part of the all-metal carriage . . . no wobbling, nor danger of instrument falling off.

Quiet, widely spaced casters provide an unusually stable stand. Permits easy movement in tight spaces . . . ample storage compartment for accessories.

The "Versa-Scribe" can be easily and quickly removed and inserted into conventional carrying case for use as a portable instrument.

The new "Versa-Scribe" Direct Writer provides dual paper speed, especially valuable in measuring time intervals.

Now more than ever is the Cambridge "Versa-Scribe" the Electrocardiograph of choice.



VERSA-SCRIBE Electrocardiograph Model VS (portable).

Send for descriptive literature

CAMBRIDGE INSTRUMENT CO., Inc.

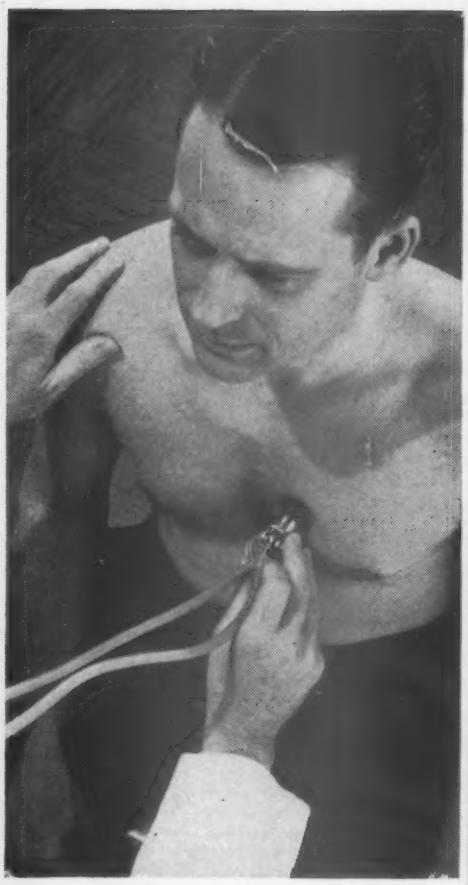
Graybar Building, 420 Lexington Ave., New York 17, N. Y. .

Cleveland 2, Ohio, 8419 Lake Avenue
Detroit 37, Mich., 13730 W. Eight Mile Rd.
Oak Park, Ill., 6605 West North Avenue
Jenkintown, Pa., 479 Old York Road
Silver Spring, Md., 933 Gist Avenue

PIONEER MANUFACTURERS OF THE ELECTROCARDIOGRAPH

CAMBRIDGE ALSO MAKES the Audio-Visual Heart Sound Recorder, Multi-Channel Recorder, Dye-Dilution Curve Recorder, Operating Room Cardioscope, "Simpli-Scribe" Direct Writer Electrocardiograph, Pulmonary Function Tester, Educational Cardioscope, Plethysmograph, Electrokymograph, Research pH Meter, Huxley Ultra Microtome, Pocket Dosimeter, and Lindemann-Ryerson Electrometer.

CAMBRIDGE
DIAGNOSTIC INSTRUMENTS



■ to improve
cardiac
function

CRYSTODIGIN®

permits
accurate dosage titration

Since initial digitalization and maintenance dosage must be carefully individualized, Crystodigin fulfills the important requirements of a preferred digitalis. Crystodigin is a crystalline-pure, uniformly potent single glycoside that is completely absorbed in the gastro-intestinal tract. With Crystodigin, the maximum therapeutic effect can be readily obtained by dosage titration in increments as small as 0.025 mg.

Available in scored tablets of 0.05 mg. (orange), 0.1 mg. (pink), 0.15 mg. (yellow), and 0.2 mg. (white); and in 1-cc. and 10-cc. ampoules, 0.2 mg. per cc.

Crystodigin® (crystalline digitoxin, Lilly)

170102

The American Journal of Cardiology

VOLUME VIII SEPTEMBER 1961 NUMBER 3

Clinical Studies

Evaluation of an Enlarged Cardiothymic Image in Infancy

Thymolytic Effect of Steroid Administration*

SYLVIA P. GRIFFITHS, M.D., O. ROBERT LEVINE, M.D., DAVID H. BAKER, M.D. *and* SIDNEY BLUMENTHAL, M.D.

New York, New York

EVALUATION OF the mediastinal image in roentgenograms of the chest is an essential component of cardiac diagnosis. The radiographic appearance of the heart and great vessels may be obscured by the thymus which may extend over the heart as an apron, occasionally approaching the diaphragm. This enlargement may be unilateral or bilateral.

An enlarged or deformed cardiothymic image in infants and children may be difficult to interpret. A wide mediastinal shadow may suggest the presence of heart disease when none actually exists. In some cases of heart disease, a wide mediastinal image may exaggerate the apparent degree of cardiomegaly. Furthermore, the thymus may obscure the silhouette of the cardiac and supracardiac vascular structures and mask valuable clues to accurate diagnosis.

This paper presents five cases which illustrate some of the diagnostic problems created by an enlarged cardiothymic image. The previously reported method[1] of producing acute involution of the thymus through the administration of adrenal corticosteroids was utilized to delineate the cardiovascular components of the mediastinum.

HISTORICAL BACKGROUND

There is a wide range in the weight of the thymus at any given age, particularly during infancy.[2] The variability in the size of the thymus, together with its marked sensitivity to endogenous and exogenous stimuli, make it impossible to determine whether an "enlarged" thymus represents a normal variant or a response to undefined physiologic influences.

The thymus gland responds to the same lytic stimuli as does lymphoid tissue in general. Although Heinecke[3] has previously noted that ionizing radiation caused involution of lymphoid structures in animals, Friedlander[4] in 1907 was the first investigator to report its application in human subjects. This technic was a standard method of shrinking the thymus until cogent arguments were raised concerning its rationale and safety.[2]

The lytic effect of adrenal cortical substance on the thymus was demonstrated in animals by Selye[5,6] in 1936. He observed that acute

* From the Babies Hospital, and Department of Pediatrics, College of Physicians and Surgeons, Columbia University. This study was supported in part by a training grant (HTS-5389) from the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

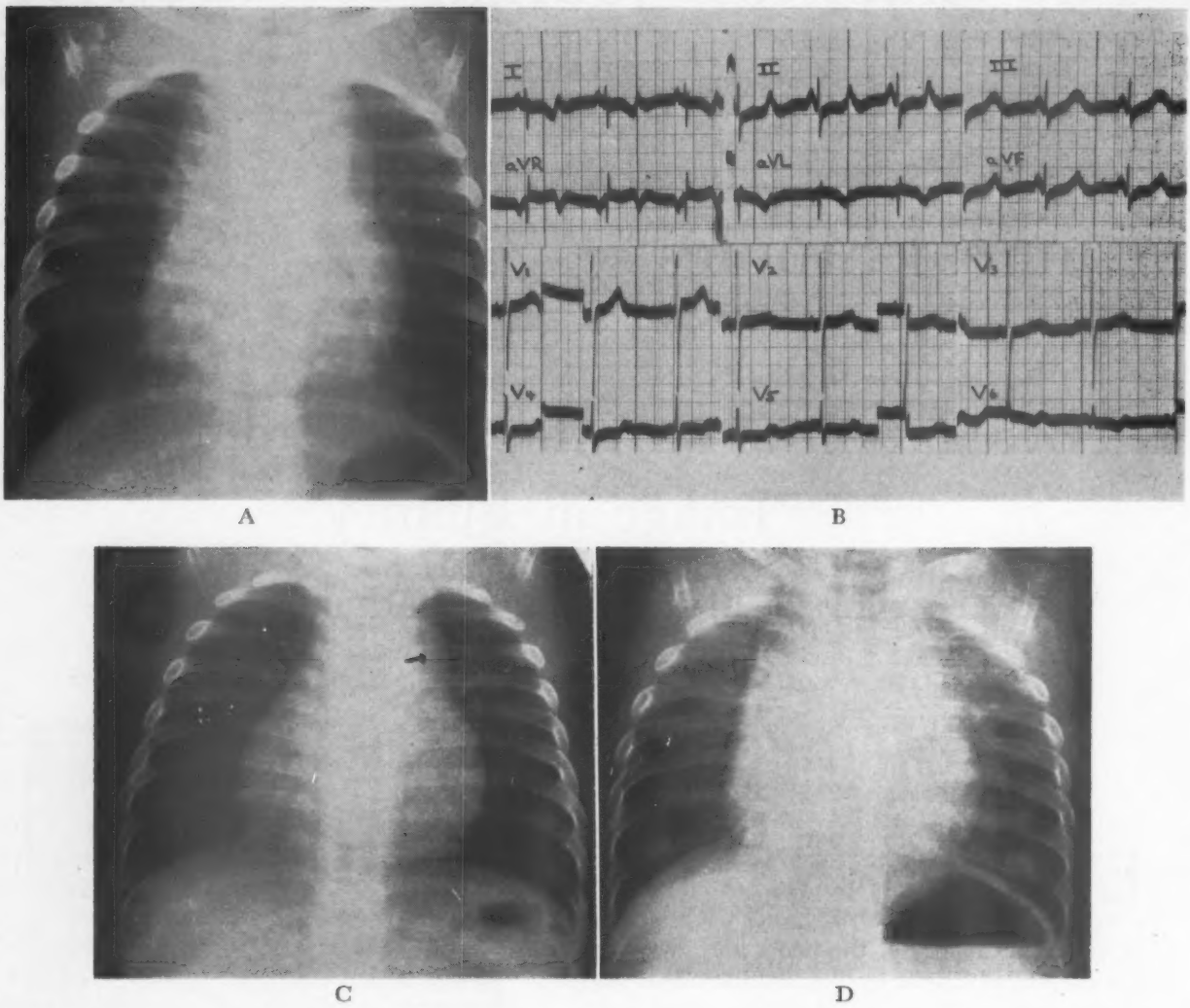


FIG. 1. Case 1. A, age three months: before treatment. B, electrocardiogram showing complete A-V heart block with rhythm arising in the bundle of His. Note T wave inversion in leads I, aVL, V_5 and V_6. The precordial leads are recorded at one-half standardization. C, dextroversion of heart and left aortic arch apparent after involution of thymus with corticosteroids. D, regrowth of thymus gland three and a half months after termination of steriod therapy.

involution of the thymus was one of the dominant features of the stereotyped alarm or stress reaction, and that it did not occur in adrenalectomized animals. Subsequently, the thymolytic effect of adrenocortical substances became a convenient and sensitive method for the bioassay of the various steroids and their derivatives.[7–12]

The fundamental mechanism by which steroids induce acute involution of lymphatic tissue is not known.[13] It has been noted[11] that the administration of steroids causes the destruction of lymphocytes and inhibition of mitosis. Although steroids have a lytic effect on lymphoid tissue in general, not all components of the lymphatic system are equally sensitive. The mature, small lymphocytes, which are characteristic of the thymus gland, are very susceptible to steroid lysis, whereas the large lymphocytes and reticuloendothelial cells, of which lymph nodes are chiefly composed, are relatively resistant.[7,12]

Clinical observations[14–16] have indicated that a reduction in the size of the thymus occurs in infants and children after the administration of adrenocorticotrophic hormone (ACTH). It was also noted by Andersen[17] that generalized atrophy of the thymolymphatic apparatus was present at necropsy in premature infants who had been treated with ACTH for retrolental fibroplasia.[1] Subsequently, the clinical use of adrenocorticosteroids specifically to induce acute

involution of the thymus has been reported.[1,18]

Presentation of Cases*

Case 1. Dextroversion of Heart Obscured by Enlarged Thymus: This male infant (S. S.) was admitted to the Babies Hospital at three months of age for cardiac evaluation prior to inguinal herniorrhaphy. A heart murmur had been heard at one month of age. At two months, he had been admitted to another hospital because of fever, cough and vomiting; bradycardia was noted on examination. He was treated for a respiratory infection with antibiotics and discharged after three days.

On admission the infant appeared alert and vigorous. Examination was noncontributory except for the right inguinal hernia and the abnormal auscultatory findings. There was a bradycardia of 68 to 80 beats per minute. A grade 3, harsh, systolic murmur was best heard at the midleft sternal border, and was widely transmitted over the precordium and to the back.

The roentgenogram of the chest (Fig. 1A) was reported as revealing an enlarged heart with a wide supracardiac shadow; the latter was thought to represent thymus. The pulmonary vascular markings were increased. These observations were consistent with cardiomegaly associated with a congenital cardiac malformation and a left to right shunt.

The electrocardiogram indicated complete atrioventricular block and a regular idioventricular rhythm arising in the bundle of His (Fig. 1B). The apparent 2:1 atrioventricular response in some leads illustrated was not consistent on long strips. The atrial rate was 140 and the ventricular rate was 71. The T waves were inverted in leads I, aVL, V_5 and V_6, upright in V_1 and flat in V_2. The P waves were upright in lead I.

Effect of Steroid Administration: A diagnosis of viral myocarditis with acquired heart block was proposed on the basis of the recent febrile respiratory illness and the abnormal changes of the T wave in the electrocardiogram. Steroids were administered in an attempt to alter either the conduction defect or the thymic shadow. Prednisone 20 mg. daily (4 mg. per kg. per day) was administered for seven days, then the dosage tapered during the next four days. This regimen produced no change in the electrocardiogram. Serial roentgenograms, however, showed progressive diminution of the large mediastinal shadow, and revealed that the heart was dextroposed with a left aortic arch (Fig. 1C). An electrocardiogram was then obtained with reversal of the left and right arm leads and placement of the precordial leads over the right side of the chest; the electrocardiographic tracings were then reviewed, and it became clear that the T wave changes originally noted were a manifestation of dextroversion of the ventricles with normally situated atria.[19] Three and a half months after steroid-induced regression of the thymus, a roentgenogram showed regrowth of the gland (Fig. 1D).

An *angiocardiogram* was performed at 13 months of age and demonstrated the following: (1) corrected transposition of the great vessels; (2) dextroversion of the ventricles with normally situated atria; and (3) an intracardiac left to right shunt, probably at the ventricular level.

Comment: This case illustrates that extensive growth of the thymus gland in a downward direction may obscure the location of the apex of the heart on the roentgenogram of the chest. In such instances, one may be deprived of helpful radiographic clues to correct diagnosis.

In this case dextroversion of the heart was first discerned on a roentgenogram of the chest after the administration of adrenocorticosteroids produced involution of the thymus. Evidence of dextroversion then provided an explanation for the abnormalities of the T wave in the electrocardiogram and made it likely that the heart block was congenital rather than acquired. The findings in this infant of complete heart block, ventricular septal defect and corrected transposition of the great vessels illustrate a recently reported triad of congenital cardiac malformations.[20]

Case 2. Enlarged Thymus Shadow Simulating Cardiomegaly: This male infant (C. H.) had been adopted during the first month of life. A heart murmur was first heard at four months which became more intense at five months of age. A roentgenogram of the chest was reported as showing "generalized cardiac enlargement consistent with the diagnosis of congenital heart disease." It was suggested that this infant be returned to the adoption agency because of the existence of a serious congenital anomaly of the heart. The infant was referred for cardiac consultation prior to this legal procedure.

Examination revealed a healthy-appearing five month old infant. The only significant finding was a grade 3, vibratory, systolic murmur which was localized to the area between the low left sternal border and the apex. An *electrocardiogram* was within normal limits. A *chest film* in the frontal view showed marked widening of the mediastinal shadow (Fig. 2A).

Effect of Steroid Administration: It was suspected that the murmur was functional in origin, and that the apparent cardiomegaly was due to a prominent thymus. In order to document the latter the infant was started on a regimen of triamcinolone 2 mg. orally twice daily (1 mg. per kg. per day) on an outpatient basis. A repeat film after three days of steroid therapy revealed marked shrinkage of the mediastinal shadow; at seven days this had decreased to about 60 per cent of its pretreatment transverse

* Cases 1 and 2 were previously reported.[1, 21]

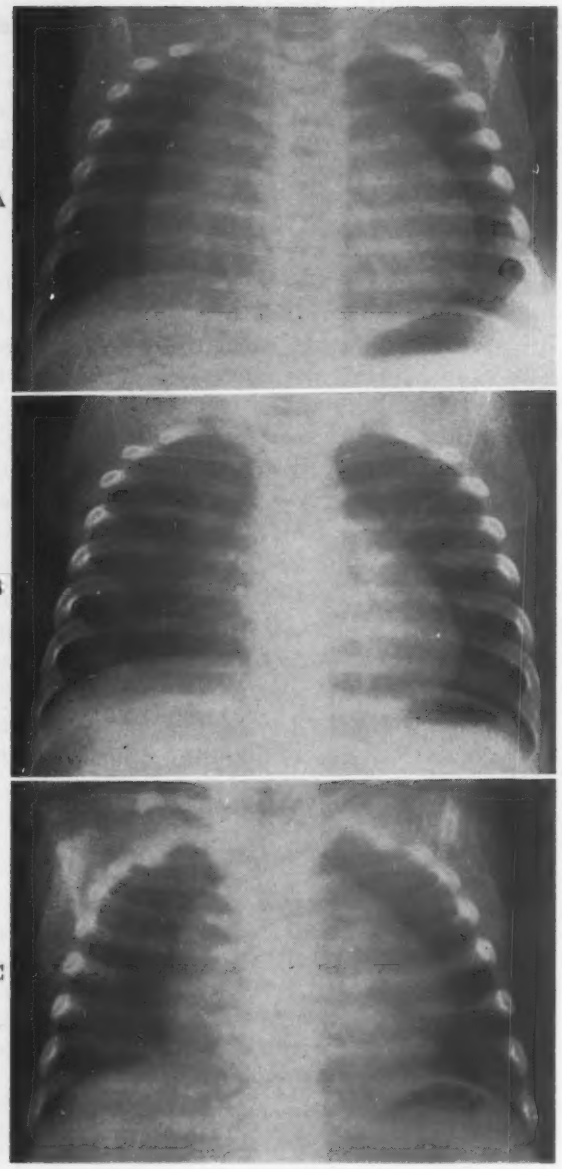


FIG. 2. Case 3. A, age five months: before treatment. B, shrinkage of cardiothymic image after one week of corticosteroid therapy. C, regrowth of thymus with enlargement of cardiothymic image two weeks after steroids were discontinued.

diameter, and steroid therapy was discontinued (Fig. 2B). A film taken two weeks later revealed evidence of regrowth of the thymus to approximately its original size (Fig. 2C).

Comment: In the case of this adopted infant a tremendous amount of anxiety was engendered by the coincidence of a loud functional murmur and an unusually large cardiothymic shadow. The simple expedient of inducing acute involution of the thymus with steroid made it possible to reassure the adoptive parents and the referring physician of the absence of cardiomegaly and implication of organic heart disease.

It was interesting to note the disparity between the size of the mediastinal image on the frontal and the lateral views. In the frontal projection there was generalized enlargement of the cardiothymic image, whereas in the lateral projection it did not appear to be abnormally wide. In the latter view, however, a shadow was present which filled the anterior-superior mediastinum. These findings suggested the presence of an enlarged thymus overlying the heart and argued against significant cardiomegaly.

Case 3. Enlarged Supracardiac Image Due to Vascular Structures: This infant (D. V.) was born prematurely, weighing 2050 gm. She sucked poorly and seemed to fatigue easily. On the third day mild puffiness of the hands, feet and periorbital tissues were noted. The infant had a brief episode of cyanosis during a feeding.

Examination revealed a short, harsh, systolic murmur heard best at the left base and transmitted posteriorly. A *roentgenogram of the chest* showed enlargement of both the cardiac and supracardiac images (Fig. 3A). An *electrocardiogram* indicated probable right ventricular enlargement as manifested by a tall R with slurred upstroke in V_3R and V_1, upright T in V_1–V_4 and a deep S in V_5–V_6.

Effect of Steroid: Because of the appearance of the wide supracardiac shadow, the possibility of total anomalous pulmonary venous drainage was raised. In order to exclude the possibility that this shadow might be thymic in origin, the infant was started on prednisone 2.5 mg. twice daily at two weeks of age (1 mg. per kg. per day). Roentgenograms taken after two, six and ten days of therapy revealed no significant change in the size or shape of the mediastinal image. It was concluded that the abnormal shadow was vascular in origin.

Diagnosis: At one month of age the infant had signs of congestive heart failure and was digitalized. Examination at this time revealed diminution in the pulse in the legs as compared to the radial pulse. This observation suggested an additional diagnosis of coarctation of the aorta. An *angiocardiogram* was performed at six weeks of age which demonstrated a left superior vena cava draining into the right atrium and coarctation of the aorta distal to the left subclavian artery (Fig. 3C and D).

The infant has done well on medical management and is being followed on an outpatient basis.

Comment: In this case the radiographic appearance of the superior mediastinal shadow resembled that of the supracardiac type of total anomalous pulmonary vein drainage. Failure of steroid to alter the appearance of the supracardiac shadow led to the correct presumption that it was vascular in origin. The similarity

in appearance of the anterior-superior mediastinal image composed either of an enlarged thymus or anomalous vascular structures has been noted in other cases. In each instance it has been possible, by the administration of steroid, to make this differentiation.

This premature infant represents the youngest and smallest patient to whom we have administered steroid for the induction of acute thymic involution. No side effects either of the drug or of its abrupt discontinuance were apparent.

Case 4. Enlarged Thymus Simulating Corrected Transposition of Great Vessel: During the neonatal period this girl (P. W.) was noted to have a loud systolic murmur which was considered to be organic in nature. A roentgenogram of the chest at three days of age showed a widened mediastinal image. The infant thrived and showed no cyanosis or dyspnea.

At one year of age an electrocardiogram indicated right axis deviation and right ventricular enlargement. A roentgenogram of the chest at this time still showed a widened mediastinal image with rounding of the left cardiac border (Fig. 4A). The auscultatory findings were consistent with a diagnosis of pulmonic stenosis.

During the second year of life, mild exertional fatigue was noted. The child was admitted to the hospital at two and one-half years of age for diagnostic evaluation. The appearance in the roentgenograms of a prominent, straight left cardiac border suggested the additional diagnosis of corrected transposition of the great vessels with laterally placed aorta (Fig. 4B). Cardiac catheterization was undertaken but because of technical difficulties incomplete data were obtained. Pulmonic stenosis and a small right to left shunt were documented.

Effect of Steroid: In an attempt to decide whether the prominent left cardiac contour was due to thymus, the child was given a five day course of prednisone, 30 mg. daily (2 mg. per kg. per day), on an outpatient basis. A roentgenogram of the chest taken after two days of therapy revealed complete disappearance of the unusual shadow (Fig. 4C).

An *angiocardiogram* was performed subsequently and demonstrated tetrad of Fallot with normal relationships of the great vessels.

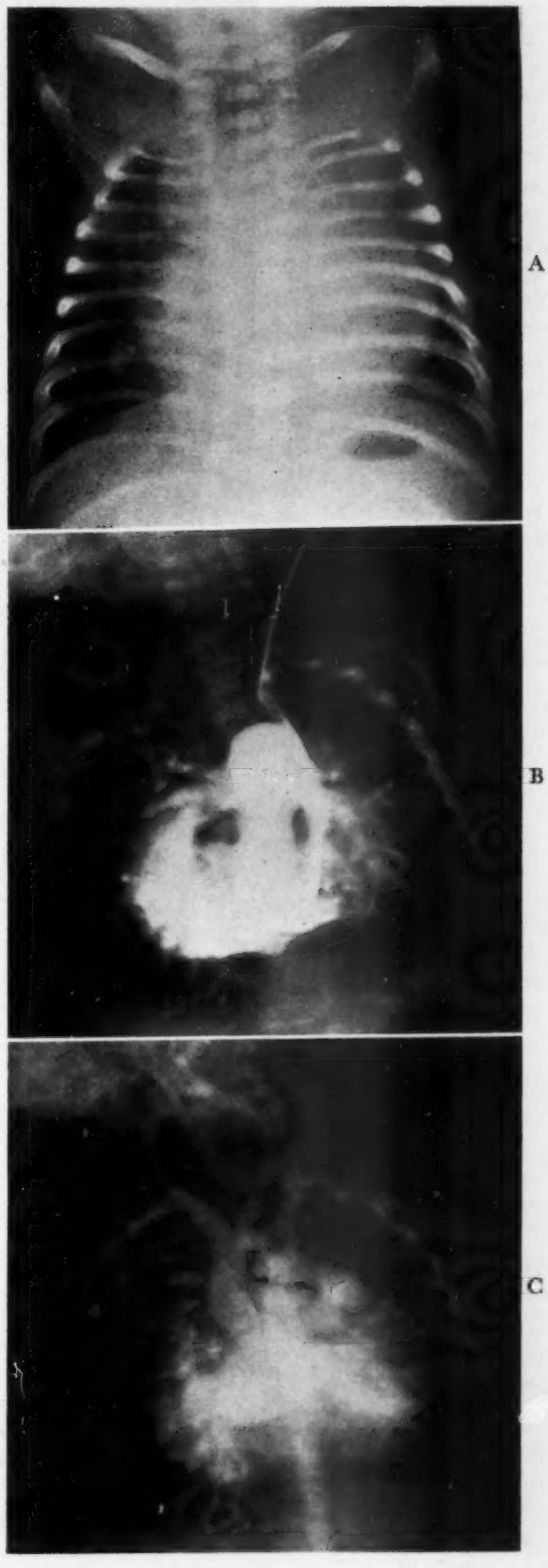


FIG. 3. Case 3. A, age two weeks: before treatment. There was no change in size of cardiothymic image after ten days of corticosteroid therapy. B, angiocardiogram at six weeks of age showing persistent left superior vena cava entering right atrium. C, film showing coarctation of the aorta (arrows).

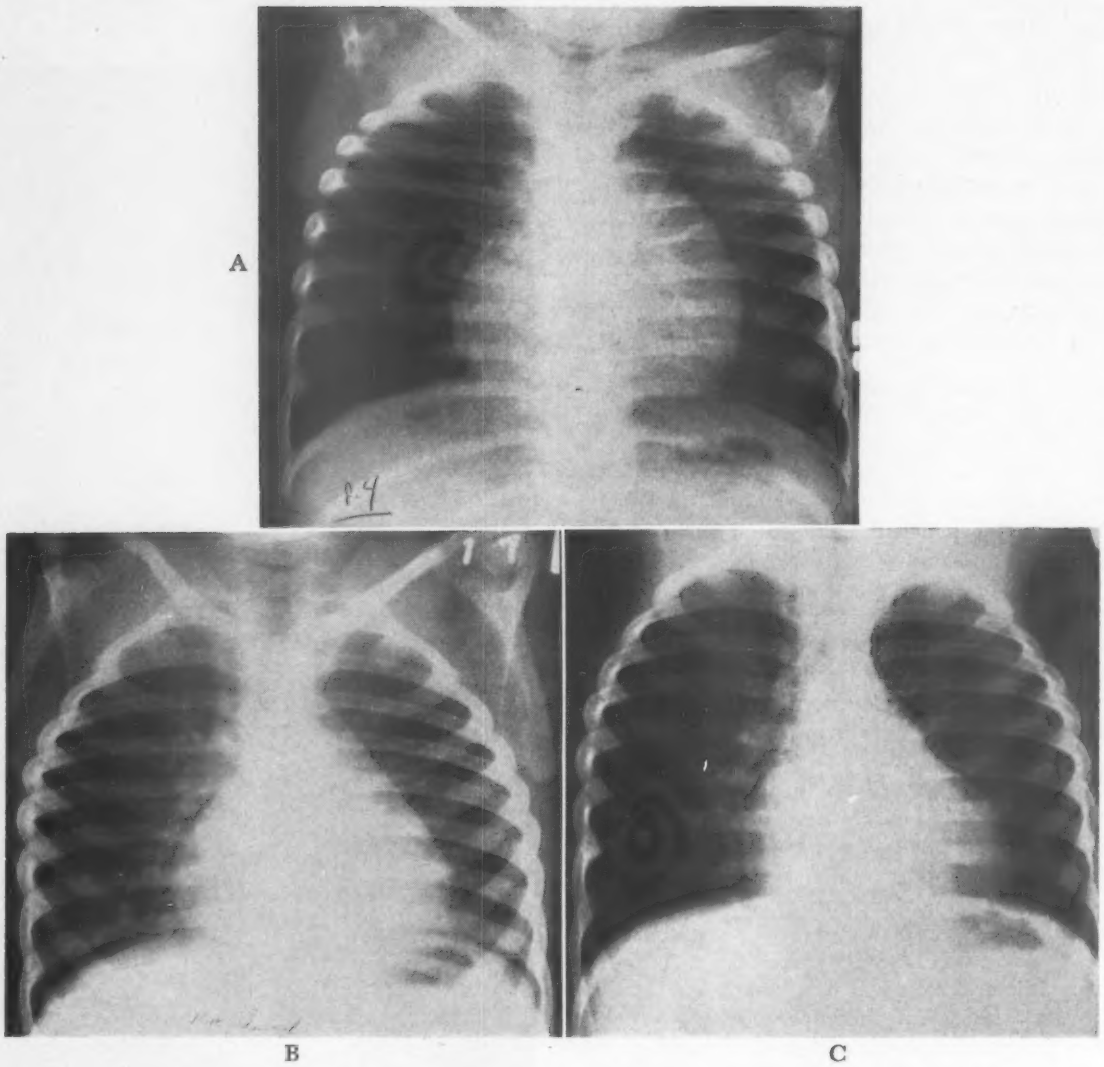


FIG. 4. Case 4. A, age three days. B, age two and one-half years showing persistence of prominent upper left heart border. C, shrinkage of left lobe of thymus after two days of corticosteroid treatment.

Comment: This child with pulmonic stenosis thrived during infancy and had only minimal fatigability as a toddler without evidence of progressive cardiac enlargement. The peculiar contour of the left border of the cardiac image resembled that seen in corrected transposition of the great vessels. Consideration had been given to the possibility that widening of the mediastinal image in the early films was due to thymus. The persistence of thymic enlargement was proved by a trial of steroid therapy at two and one-half years of age.

The problems created by thymic enlargement in evaluation of the roentgenogram of the chest in congenital heart disease are not limited to the infant age group.

Case 5. Spontaneous Shrinkage of Enlarged Thymus: This infant (T. C.) was referred to the Pediatric Clinic at two months of age because of a heart murmur. She had been thriving and had otherwise seemed entirely well.

Examination revealed a grade 3, harsh, systolic murmur heard maximally in the pulmonic area. An *electrocardiogram* indicated no axis deviation and a tall R with slurred upstroke in V_3R and V_1. The *roentgenogram* of the chest showed marked widening of the mediastinal image with normal pulmonary vascularity (Fig. 5A). The auscultatory and electrocardiographic findings were consistent with a diagnosis of pulmonic stenosis.

The infant was followed at regular intervals in the Cardiac Clinic. A roentgenogram of the chest at ten and one-half months showed a marked decrease in width of the mediastinal shadow; the cardiac image was now normal in appearance (Fig. 5B). During the eight and one-half months between the two roentgenographic examinations the patient had received no steroids and had been entirely well.

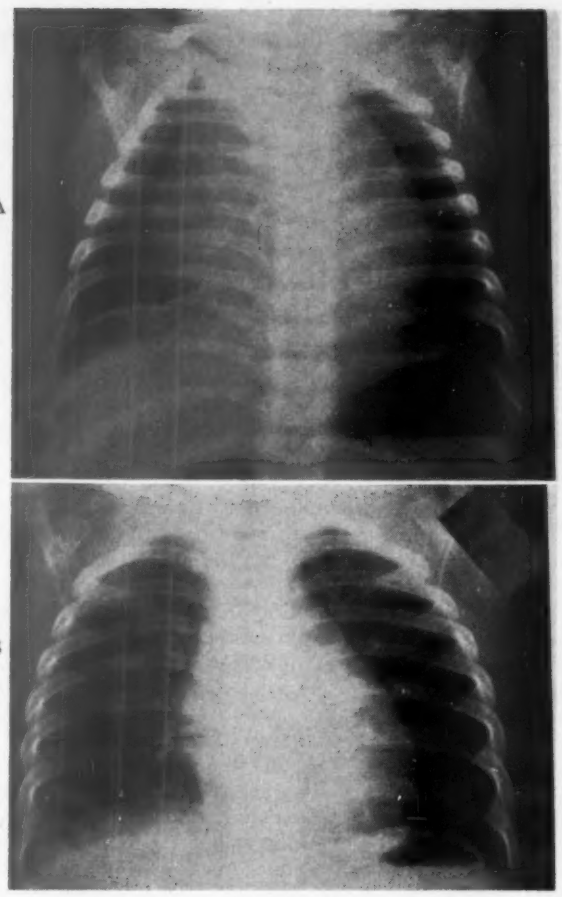


FIG. 5. Case 5. A, age two months. B, age ten and one-half months showing spontaneous shrinkage of cardiothymic image.

Comment: This case is of particular interest as a demonstration of spontaneous shrinkage of the thymus during infancy. It further points up the care that must be taken in the interpretation of serial chest films in observing the "natural" course of cardiac anomalies during this age period.

COMMENTS

The size and configuration of the mediastinal image may be markedly influenced by the manner in which roentgenograms of the chest are obtained. Factitious widening or distortion of the image in the frontal and lateral projections may result from films taken with the patient in the recumbent position, or from malposition of the patient into a slightly oblique view.[2,21] There may be marked variation in the size and contour of the cardiothymic image during the phases of the cardiac and respiratory cycles. These observations have frequently been made during fluoroscopy, and more recently by cinefluoroscopy and angiography in normal newborn infants at rest and during crying.[22]

An enlarged mediastinal image on roentgenographic examination, despite optimal technic, may be difficult to interpret when it is not possible to define clearly its thymic, cardiac and vascular components. When a widened, deformed image is apparent in the frontal projection, examination of the chest films in the lateral and oblique views may occasionally elucidate its components. Observations at fluoroscopy may clarify the situation in some cases. In many instances, however, the thymus gland, the heart and the supracardiac vascular shadows cannot be separated. The problems of interpretation of a widened mediastinal image are most commonly encountered during infancy, but may, on occasion, occur in childhood.

Diagnostic Value of Administration of Corticosteroids: The diagnosis and management of patients with real or suspected heart disease may be influenced by the finding of an abnormal cardiothymic image. In selected cases where an enlarged thymus is suspected as contributory to the deformed image and masking the true roentgenographic appearance of the heart and great vessels, adrenal glucocorticoid derivatives may be of value in producing involution of the gland.

The administration of a five to seven day course of adrenal glucocorticoid derivative has constituted a safe and effective thymolytic technic. Observations have been made in approximately twenty cases in infancy or childhood, four of which are illustrated in this paper (Cases 1 to 4). We have used both prednisone and triamcinolone without any discernible difference in effect. The dosage used has been empirical; satisfactory results have been achieved with an oral daily dose equivalent to 5 mg. per kg. of cortisone. For the purposes of this study, a roentgenogram was usually obtained after two to three days of treatment to ascertain initial drug effect, another at the end of the five to seven day treatment period to visualize maximal thymolytic effect and a follow-up film in two to three weeks to observe the extent of regrowth of the thymus. We recommend, however, that only a single frontal film be taken at the end of a one week course of treatment for differential diagnosis in most cases. It should be noted that the average radiation exposure from a single roentgenogram of the chest is 10 milliroentgens as an air dose

to the patient's back; the total dose of ionizing radiation ordinarily required to effectively shrink the thymus gland is in the range of 40 to 200 roentgens.[23]

The "rebound" phenomenon, with regrowth of the thymus gland following termination of steroid administration, is an ill defined aspect of the relationship between the thymolymphatic system and the adrenal cortex.[14] A number of cases have been observed in which the size of the cardiothymic image at the end of the rebound phase is considerably larger than at the beginning of steroid treatment.[1,24]

Summary

The relative contribution of the thymus and of cardiovascular structures to an enlarged or deformed mediastinal image on a roentgenogram of the chest may be difficult to evaluate in infants and children.

Five cases are presented which posed problems in diagnosis: in the first, the thymus obscured the presence of dextroversion of the heart; in the second, the thymus widened the mediastinal image and gave the impression of cardiomegaly and hence of heart disease, where none existed; in the third, vascular structures including a persistent left superior vena cava were responsible for the deformed supracardiac image; in the fourth, an enlarged left lobe of the thymus resulted in distortion of the left heart border and the erroneous impression of corrected transposition of the great vessels; and in the fifth, an enlarged cardiothymic image in an infant with congenital heart disease decreased in size by spontaneous shrinkage of the thymus.

The administration of adrenal glucocorticoid derivatives is suggested for the induction of temporary involution of the thymus gland in selected cases. This technic is of value when there is need to clarify the composition of an unusual cardiothymic image in order to estimate the size and configuration of the heart and great vessels.

References

1. Caffey, J. and DiLiberti, C. Acute atrophy of the thymus induced by adrenocorticosteroids, observed roentgenographically in living human infants. *Am. J. Roentgenol.*, 82: 530, 1959.
2. Caffey, J. The Thymus, p. 320. Nelson Loose-Leaf Medicine. New York, 1942. Thomas Nelson & Sons.
3. Heinecke, H. Ueber die Einwirkung der Roentgenstrahlen auf Tiere. *München. med. Wchnschr.*, 50: 2090, 1903.
4. Friedlander, A. Status lymphaticus and enlargement of the thymus, with report of a case successfully treated by the x-ray. *Arch. Pediat.*, 24: 490, 1907.
5. Selye, H. A syndrome produced by diverse nocuous agents. *Nature*, 138: 32, 1936.
6. Selye, H. Thymus, adrenals and thyroid in the response of the organism to certain drugs. *Am. J. Physiol.*, 116: 141, 1936.
7. Dougherty, T. F. Effect of hormones on lymphatic tissue. *Physiol. Rev.*, 32: 379, 1952.
8. Dorfman, R. I., Dorfman, A. S. and Laubach, G. Thymolytic activity of 14-alpha-hydroxycortisol. *Proc. Soc. Exper. Biol. & Med.*, 100: 69, 1959.
9. Kline, I. T. Studies on squalene potentiation of thymic response to corticotropin. *Endocrinol.*, 63: 335, 1958.
10. Rerup, C. The bioassay of corticotropin A. *Acta endocrinol.*, 29, supp. 42, 1958.
11. Santisteban, G. A. and Dougherty, T. C. Comparison of the influences of adrenocortical hormones on the growth and involution of lymphatic organs. *Endocrinol.*, 54: 130, 1954.
12. Santisteban, G. A. Adrenocortical influences upon the reconstitution of lymphatic tissue following acute involution. *Endocrinol.*, 64: 638, 1959.
13. Lundin, P. N. Anterior pituitary gland and lymphoid tissue growth. *Acta endocrinol.*, 28, supp. 40, 1958.
14. Soffer, L. J., Gabrilove, J. L. and Wolf, B. S. Effect of ACTH on thymic masses. *J. Clin. Endocrinol.*, 12: 690, 1952.
15. Torsoli, A. and Sarteschi, G. Studi sul timo: effete della somministrazione di ACTH e forma e il volume dell'organo. *Folia enco. (Pisa)*, 5: 667, 1953.
16. Perez-Moreno, B. Tratamiento hormonal de la hipertrofia timica. *Acta pediat. espanola*, 15: 619, 1958.
17. Andersen, D. H. Personal communication. Quoted in reference 1.
18. Blumenthal, S., Caffey, J. and Griffiths, S. P. Effect of adrenocortical steroid in the radiologic differentiation of an enlarged mediastinal image. Abstract submitted to Am. Heart Assoc. 32nd Scientific Session. *Circulation*, 20: 674, 1959.
19. Grant, R. P. Syndrome of dextroversion. *Circulation*, 18: 25, 1958.
20. Walker, W. J., Cooley, D. A., McNamara, D. G. and Moser, R. H. Corrected transposition of the great vessels, atrioventricular heart block, and ventricular septal defect: A clinical triad. *Circulation*, 17: 249, 1958.
21. Shapiro, A. V. and Bell, L. Study of the "widened" mediastinum in children and pitfalls in diagnosis. *Am. J. Roentgenol.*, 49: 159, 1943.
22. Burnard, E. D. and James, L. S. The newborn cardiac silhouette in newborn infants. A cinematographic study of the normal range. *Pediatrics*, 27: 713, 1961.
23. Laughlin, J. S., Meurk, M. L., Pullman, I. and Sherman, R. S. Bone, skin and gonadal doses in routine diagnostic procedures. *Am. J. Roentgenol.*, 78: 961, 1957.
24. Caffey, J. and Silbey, R. Regrowth and overgrowth of the thymus after atrophy induced by the oral administration of adrenocorticosteroids to human infants. *Pediatrics*, 26: 762, 1960.

Preoperative Diagnosis of Acquired Valvular Disease

Evaluation of Different Diagnostic Methods with Special Emphasis on Left Heart Catheterization and Comparison with Surgical Findings*

DANIEL E. DUTREY, M.D. *and* ELLET H. DRAKE, M.D.

Detroit, Michigan

PRIOR TO the successful surgical treatment of acquired valvular disease, diagnosis was accomplished principally by history and the various technics of physical examination, of which auscultation gave the most definitive information. Emphasis was placed upon a qualitative diagnosis based on the presence or absence of murmurs at the various valvular areas. There was a tendency toward constant repetition of certain mistakes, which is not surprising since the only method of checking diagnostic acumen was through postmortem examination, which might or might not be available several years later, at which time the original picture would have been altered by progressive disease and complications. Although the Graham Steell murmur was faithfully described in medical texts, the presence of a blowing diastolic murmur along the left sternal border was commonly interpreted as representing some degree of aortic insufficiency. The mere presence of a systolic blow in the mitral area usually was interpreted as mitral insufficiency. In addition, there were occasional cases of mitral stenosis called "cor pulmonale" principally due to the absence of a diastolic rumble at the apex, despite possible roentgenographic evidence of an enlarged left atrium.

These errors in diagnosis were not so important when the patients were treated symptomatically, from the standpoint of their complications, but with the advent of specific therapy of the valvular lesion, it became most important not only to establish specifically what valves were involved, but also, even more important, to quantitate the diagnosis with respect to the type of lesion present. This quantification may be quite difficult from physical examination alone, both in the presence of involvement of more than one valve and in cases of combined lesions of a single valve. Here, the accuracy of the diagnosis will determine the decision as to whether the patient will be subjected to surgery and equally as important, whether that surgery is to be a simple commissurotomy or a complicated open operation employing the heart-lung bypass. It is the purpose of this paper to compare the results of certain accessory diagnostic aids, particularly left heart catheterization, with the impression obtained by physical examination and with the situation as encountered by the surgeon at operation. Our paper deals with ninety-nine cases, selected from our entire series of left heart catheterization on the basis of the fact that the patients eventually were subjected to surgery (ninety-six cases, with autopsy in thirteen) or autopsy alone (three cases).

We are well aware of the possible sources of error in accepting the surgeon's opinion as final in establishing a diagnosis. Accurate estimation of valvular area by palpation at the time of surgery is a difficult feat at best. In addition, the abnormal state created by anesthesia and an open chest undoubtedly alters the picture which existed prior to operation, and probably particularly complicates the ability to detect the presence of small degrees of mitral insufficiency. Despite these shortcomings, the estimation had considerable com-

* From the Division of Cardiovascular Disease, Henry Ford Hospital, Detroit, Michigan.

parative value, particularly when reported by the same surgical team with a large experience.

Operative Evaluation of Valvular Lesions

The severity of the lesion was graded according to the impression of the surgeon in his operative note as follows:

MITRAL STENOSIS

1. 0, a valve that admits approximately two and one-half fingers, *no appreciable stenosis*.
2. 1+, a valve that admits approximately one and one-half to two fingers. The surgeons usually describe such a valve as exhibiting *minimal mitral stenosis*.
3. 2+, a valve admitting approximately one to one and one-half fingers, usually described as *moderate mitral stenosis* by the surgeons.
4. 3+, a valve that barely admits one finger, usually described as *tight stenosis*.
5. 4+, a valve that does not admit the tip of the finger, usually described as *very tight stenosis*.

MITRAL INSUFFICIENCY

1. 0, *no* insufficiency detected.
2. 1+, described by the surgeon as a *very small* regurgitant jet.
3. 2+, *appreciable* regurgitant jet.
4. 3+, a *considerable degree* of mitral insufficiency present.
5. 4+, *severe* mitral insufficiency (including cases of "pure" insufficiency).

When both insufficiency and stenosis were present in significant degree, the surgeon was asked specifically to give an opinion as to which was the predominant lesion. In only two cases did they consider that there were equal degrees of the two conditions present.

AORTIC STENOSIS

No cases of absent or minimal aortic stenosis were operated upon for this condition, the patients undergoing surgery all having lesions which were described in the operative report as "tight stenosis." Many of these, however, were operated by a transventricular approach where the surgical opinion had to be given without the benefit of manual palpation. No cases in which insufficiency was considered to be the predominant lesion of the aortic valve are included in this study.

OTHER VALVULAR LESIONS

Although the diagnosis of *tricuspid and pulmonary insufficiency* appeared many times in the preoperative diagnosis (the former in some cases being supported by right heart catheterization data) all were considered to be relative to primary pathology in the mitral or aortic valve, with one exception. This case was one of *organic tricuspid stenosis and insufficiency* in association with mitral stenosis and a bivalvular commissurotomy was carried out.

Methods of Diagnosis

CLINICAL

The clinical impression was obtained by evaluating the statements in the medical history after physical examination was completed. Due to our institutional arrangement, the patient was commonly examined by several observers, and in many cases some disagreement as to minor details was present among the examiners. Because of this fact, it was sometimes difficult to decide on a final clinical impression for the purpose of this study; in these cases, we gave more weight to the opinion of the more experienced observers.

Classification of Results: The accuracy of the clinical opinions were classified as follows:

In agreement, when the clinical impression agreed entirely with the final result observed at surgery or postmortem.

Equivocal, when the severity of the lesion, estimated clinically, did not coincide with the result of surgery or when the clinical impression failed to make a definite statement as to which lesion predominated. Such a clinical opinion does not imply an error in diagnosis and was usually accompanied by a request for further diagnostic studies. The final opinion, taking into consideration such studies, was usually entirely correct.

In disagreement, those cases in which a definite diagnosis was made clinically and not found to be present or those in which a significant valve lesion was missed.

No detailed gradation of a specific lesion was attempted on the basis of clinical examination alone.

RADIOLOGY

This method included *roentgenograms* in four views with barium fluoroscopy, and *laminography* to determine the presence or absence of calcium in the regions of the mitral and aortic valves. The accuracy of this diagnostic aid was evaluated according to the report of individual chamber enlargement and the condition of the lung fields. Enlargement of the left atrium, right ventricle and main pulmonary artery, together with peripheral evidence of pulmonary hypertension, was considered as pointing to a diagnosis of mitral stenosis. The addition of left ventricular enlargement, in the absence of hypertension or aortic valve lesion, was thought to suggest some degree of mitral insufficiency. Left ventricular enlargement alone, with or without the presence of calcium, favored an aortic lesion alone or mitral insufficiency. In addition to enlargement of the chambers, the vascular picture, including the arterial pattern, degree and location of venous distention, and the presence or absence of Kerley's lines, was taken into consideration in formulating a definitive opinion.

Classification of Results: The results of the x-ray evaluation were classified as follows:

Good correlation, when the x-rays agreed entirely with the results found at surgery or postmortem.

Fair correlation, when the results of x-ray examination were not entirely conclusive regarding enlargement of the chambers in combined lesions, such as a report of "questionable" or "minimal" left ventricular enlargement when definite mitral insufficiency was found to be present.

Poor correlation, when the x-ray opinion was actually misleading because it did not show signs of one of the lesions later found to be present in significant degree at postmortem examination or surgery, or when signs pointing toward a specific lesion were present and this lesion was absent at surgery or autopsy.

ELECTROCARDIOGRAPHY

The electrocardiographic examinations included twelve leads, the precordial leads being recorded at double speed (50 mm. per second). Special chest leads (V_3R, V_4R, V_7 and V_8) were taken in many cases.

Classification of Results: The results of electrocardiographic examination were graded principally according to the demonstration of hypertrophy of various chambers, in much the same way that x-ray examination was evaluated.

Good correlation, when there was complete agreement with the results found at surgery, such as the demonstration of hypertrophy of both ventricles in combined valvular lesions.

Fair correlation, when there was only a suggestion of hypertrophy of one chamber in cases where the lesion was declared as being significant at surgery.

Poor correlation, in which the electrocardiogram was not helpful in that it showed normal curves or nonspecific changes, such as atrial fibrillation, or when it was actually misleading in that it indicated evidence of hypertrophy which was not verified at surgery or postmortem.

CARDIAC CATHETERIZATION

This study covered two and a half years of experience with left heart catheterization. During this time, there has been considerable change in our methods of evaluation of pressure curves, particularly regarding mitral insufficiency. Whenever possible, we have applied these newer concepts in retrospect to the older tracings, although we could not, of course, alter our previous opinion for or against operation given at the time of the original evaluation. Actual measurements of valvular area were not done routinely as the values for cardiac output are generally considered to be unreliable in the presence of significant degrees of insufficiency, rendering the estimations of area misleading in situations where they are most needed. Contrast and dye studies are now in use, but there are insufficient data available from these methods for inclusion in this paper.

Measurements and Data: The following information was obtained from left cardiac catheterization which was carried out using the conventional posterior right paraspinal approach as proposed by Bjork and modified by Fisher.[1,2]

(1) *Mean atrial pressure.*

(2) *Evaluation of V wave heights* and comparison with the height of the C wave (or A wave if this exceeded the C wave in height). A though their methods differed slightly, such measurements form the basis for the method of Allison and Linden,[3] Fisher,[1] and others.

(3) *Analysis of the degree of rapidity of the Y descent.* This formed the basis for the method employed by Owen and Wood,[4] and later modified by Morrow and his associates,[5] whose specific formula we employed.* In cases in which atrial fibrillation was present, the Morrow method was applied to the first tenth of a second of Y descent.

(4) *Evaluation of the corrected X descent*, as proposed by Wells.[6,7] In this method, the height of the C wave is subtracted from the pressure measured at the bottom of the X descent. When the X descent is not well visualized, the pressure at the end of the first third of systole is used.

(5) *Estimation of the mitral gradient* by comparison of the mean atrial pressure with the early diastolic ventricular pressure (just after the dip). We also carried out a comparison of the atrial diastolic pressure with the corresponding ventricular pressure by superimposition of the tracings utilizing the electrocardiogram. In cases of atrial fibrillation we determined the average diastolic ventricular pressures for ten cycles.

(6) *The value of the end diastolic pressure in the left ventricle* was used to estimate left ventricular failure in the absence of significant aortic insufficiency. A value of 9 mm. Hg was taken as indicating the upper limit of normal.

Classification of Results: Catheterization results were classified as follows:

(1) *Good correlation*, when they were in agreement with the results obtained at surgery or autopsy.

(2) *Fair correlation*, when they agreed with the surgical or autopsy result as to the main lesion, but varied slightly as to severity.

(3) *Poor correlation*, when the principle lesion determined by catheterization was not the principle lesion described by the surgeon or when a lesion was found at catheterization and not considered significant but was later proved to have definite significance at surgery, even though it was not the predominant lesion.

$$* \frac{P_1 - P_2/T_2 - T_1}{\text{MLAP}}$$

P_1 = Pressure at peak of V wave. P_2 = Pressure at termination of Y descent. T_1 = Time at peak of V wave. T_2 = Time at termination of Y descent. MALP = Mean left atrial pressure.

Clinical Material

Predominant Mitral Stenosis: Our surgery and autopsy experience included ninety-nine patients of which seventy-six proved to be cases of predominant mitral stenosis. These had associated complicating valvular lesions as follows: (1) Six had associated significant aortic stenosis, treated surgically. (2) Sixteen had no mitral insufficiency at all. (3) Forty-nine had 0 to + mitral insufficiency. (4) Eleven had associated significant mitral insufficiency (2+ or 3+).

Combined Mitral Stenosis and Insufficiency: Of our total cases, fourteen were considered to be cases of combined mitral lesions exhibiting significant degrees of both stenosis and insufficiency (2+ or more of each). These were further subdivided as follows: (1) Eleven cases of predominant stenosis with significant insufficiency (previously described in "4" under predominant mitral stenosis). (2) Two cases in which the surgeons considered stenosis and insufficiency to be present in equal degree. (3) One case of predominant insufficiency with 2+ stenosis.

Predominant Mitral Insufficiency: In our total of ninety-nine patients, ten were considered to have mitral insufficiency as the predominant lesion and in only one of these was a significant degree of stenosis associated (see "3" under combined lesions).

Aortic Stenosis: This condition was considered to be the only lesion in eleven cases.

Correlation of Surgical Results with Preoperative Evaluation

Mitral valvular lesions with stenosis predominating (seventy-six cases)

Clinical Evaluation: The initial clinical diagnosis was considered to show complete correlation in ten and to suggest the need for additional laboratory confirmation in the remaining sixty-six, in order to complete the quantification prior to surgery. In that group in which, despite a diagnosis of predominant stenosis, an appreciable degree of insufficiency was found to be present (eleven cases), the initial clinical impression was more often completely correct than in the group with minimal insufficiency. In rating the accuracy of the clinical examination, it should be emphasized that this series includes only those patients subjected to left heart catheterization, which was not a routine procedure in selecting patients for surgery. For the most part, cases in which catheterization is done are those in which the clinical examination is considered to be inconclusive or in which some phase of the clinical, roentgenologic and electrocardiographic examination is in disagreement.

X-ray Examination: Of the seventy-six cases having predominant mitral stenosis, fifty-nine were found to show either none or a 0–1+ associated insufficiency and no associated aortic lesion (Table 1). In thirty-five of these, the x-ray diagnosis was entirely correct. In another six, there was a questionable enlargement of the left ventricle reported, without subsequent demonstration of any insufficiency. In the remaining eighteen, left ventricular enlargement was reported to be present to a degree indicating significant insufficiency and these were considered to show poor correlation.

Electrocardiography: Of the fifty-nine cases cited previously under roentgenology as showing either none or an insignificant amount of insufficiency, the electrocardiogram was considered as showing good correlation in eleven and to be of no help in forty-eight (Table 1). In most of the latter cases the findings were nonspecific, but in four instances the electrocardiogram was reported as showing evidence of left ventricular hypertrophy, pointing to a mitral insufficiency not found at surgery or postmortem.

Mixed mitral lesions with significant degrees of both stenosis and insufficiency

As indicated, fourteen cases showed significant degrees of both lesions. This was suspected correctly on a clinical basis seven times, while in the other seven patients either one or the other lesion was considered definitely predominant with an insignificant degree of the other. Radiology showed good correlation in ten and was not helpful in four. The electrocardiogram was correct twice, and of no help in the remaining twelve (Table 1).

Mixed mitral lesions with insufficiency predominating

Of the ten cases in this category, the clinical impression was correct seven times and inconclusive three times. The electrocardiogram correlated well in four and was not helpful in six. Radiology showed good correlation in eight and was not helpful in two (Table 1).

Aortic stenosis

Of the seventeen cases of aortic stenosis in which operation was performed, all were clinically suspected of having a significant lesion. Of these, x-ray examination showed a positive correlation in fourteen and was inconclusive in three, while the electrocardiogram was helpful in twelve and of no help in five (Table 1).

TABLE I
Summary of the Results of Laboratory Aids

Surgical Classification	Specific Laboratory Aid	Good to Fair Correlation—Helpful in Making Correct Diagnosis	Poor Correlation—Not Helpful or Actually Misleading	Total
"Pure" stenosis plus cases of stenosis with 0–1+ MI	X-ray	41	18	59
	ECG	11	48	59
All cases of predominant MS	Left heart catheterization	73	3	76
Significant degrees of MS and MI	X-ray	10	4	14
	ECG	2	12	14
	Left heart catheterization	14	...	14
Predominant MI	X-ray	8	2	10
	ECG	4	6	10
	Left heart catheterization	7	3	10
Aortic stenosis	X-ray	14	3	17
	ECG	12	5	17
	Left heart catheterization	17	...	17

LEFT HEART CATHETERIZATION

Mean Left Atrial Pressure: In cases of surgically proved predominant stenosis, the average mean atrial pressure was 23 mm. Hg. Values for the other surgical groups are listed in Table II. As has been pointed out, there is nothing sufficiently distinctive about the mean atrial pressure alone to make it of diagnostic value.

Left Ventricular End Diastolic Pressure: In the cases of predominant mitral stenosis, values for the end diastolic pressure in the left ventricle are shown in Table III. It is apparent that as the severity of the component of insufficiency increases, the end diastolic pressure, in the absence of an aortic lesion, also increases, although this increase is too slight to be of diagnostic value.

Mitral Valve Gradient: Of the seventy-six cases showing *predominant mitral stenosis* at surgery, the severity of the lesion was correctly predicted at catheterization in seventy-two, while in three cases catheterization failed to reveal a significant stenotic gradient and one showed a stenosis of lesser degree than was found to exist at operation (Table I). Analysis of the three cases in which the catheter failed to demonstrate significant stenosis revealed that in one case the cardiac output was very low, in another the tracing was of very poor quality,

TABLE II
Mean Left Atrial Pressures in the Various Surgical Categories of Mitral Valvular Involvement

Surgical Lesion	Average Mean Atrial Pressure (mm. Hg)
Predominant stenosis	23
Predominant stenosis with 0–1+ insufficiency	22.2
Combined stenosis and insufficiency	24
Predominant insufficiency	19.7

TABLE III
Left Ventricular End Diastolic Pressure in the Various Surgical Categories of Mitral Valvular Disease

Surgical Lesion	Total Number	Average End Diastolic Pressure (mm. Hg)	Number Greater than 10 mm. Hg
"Pure" mitral stenosis (eliminating aortic lesions)	14	8.2	3 (21.5%)
Predominant stenosis with 0–1+ insufficiency	52	9.3	12 (23%)
Combined stenosis and insufficiency	14	11.1	7 (50%)
Insufficiency	10	12.8	5 (50%)

TABLE IV
Three Patients Considered to Have Predominant Mitral Stenosis in Whom the Surgical Findings Indicated Predominant Insufficiency

Case No.	Pre-surgical Diagnosis	Mean Atrial Pressure (mm. Hg)	V minus C (or AC) (mm. Hg)*	Wells X Descent†	Morrow Modification‡	Left Ventricular End Diastolic Pressure (mm. Hg)	Electrocardiogram	X-ray Examination Including Fluoroscopy	Surgical Diagnosis
1	MS 2+ MI 1+	24	4	3	2.3	12	LVH	LA LV RV	MI 3+ MS 2+
2	MS 2+ MI 0	18	Less than 3	2	2.3	10	Normal	RV LA	MI 3+ MS 1+
3	MS 2+ MI 0	14	Less than 3	2	3.0	8	LVH	LA LV RV	MI 2+ MS 1+

* Value over 3 mm. Hg indicates some mitral insufficiency.
† Value of 5 or more was taken to indicate severe mitral insufficiency.
‡ Value of 4 or more was taken to indicate predominant mitral insufficiency.
MS = mitral stenosis. MI = mitral insufficiency. LVH = left ventricular hypertrophy. LA = left atrial enlargement. LV = left ventricular enlargement. RV = right ventricular enlargement.

and in the third, in which the stenosis was incorrectly predicted as to severity, the patient had congestive failure and atrial fibrillation. No associated insufficiency in this latter patient was demonstrated at operation.

In the patients showing *predominant insufficiency*, the catheter diagnosis as to the degree of complicating stenosis was correct seven times and incorrect three times (Table 1). In one of these three cases, the tracing revealed a significant gradient when no stenosis existed. In another case some moderate stenosis was found at surgery although the catheter did not reveal it, and in a third case the catheterization data indicated the stenotic component to be more severe than actually proved to be the case.

In the fourteen patients with *combined mitral lesions* the magnitude of stenosis was correctly predicted in all, as it was in those cases in which there was said to be no involvement of the mitral valve (cases of pure aortic stenosis) (Table 1).

In the evaluation of mitral stenosis, the correct degree of the lesion could be predicted with about equal accuracy using either the diastolic atrial pressure or the mean atrial pressure for comparison with the ventricular diastolic values. Almost invariably, cases that were incorrectly diagnosed by one method were not diagnosed by the other.

Corrected X Descent: In applying the method of Wells,[6,7] which employs the corrected X descent in the evaluation of stenosis, our results were far less satisfactory than with the criteria mentioned above. In predominant stenosis, fifty-nine were correct and seventeen incorrect. In the ten cases of insufficiency, five were correct and five incorrect. In the combined lesions, eleven were right and one incorrect, in that the result indicated predominant insufficiency when stenosis was the main lesion. In the two cases in which stenosis and insufficiency were considered by the surgeons to be of equal degree, the Wells method showed predominant stenosis in both instances. In the patients in whom there was considered to be no involvement of the mitral valve, nine fell within the stenotic range and two in the insufficiency range.

Y Descent; V/AC Ratio Method: Evaluation of the presence or absence of mitral insufficiency in the face of predominant stenosis was quite successful, whether the V/AC ratio analysis[1,3] was employed or the Morrow method[5] applied to determine the predominant lesion. By the first method, seventy-two measurements were right and four wrong, in that they showed a degree of insufficiency not found at operation. In the cases of predominant insufficiency, seven cases out of ten were correctly predicted and three were incorrect. Out of the fourteen cases of combined lesions, nine were correctly

TABLE V

Four Patients with Predominant Mitral Stenosis in Whom the Degree of Complicating Mitral Insufficiency Was Incorrectly Predicted

Case No.	Presurgical Diagnosis	Mean Atrial Pressure (mm. Hg)	V minus C (or AC) (mm. Hg)*	Wells X Descent†	Morrow Modification‡	Left Ventricular End Diastolic Pressure (mm. Hg)	Electrocardiogram	X-ray Examination Including Fluoroscopy	Surgical Diagnosis
1	MS 4+ MI 0	22	Less than 3	2	1.3	18	Atrial fibrillation	LA RV LV	MS 3+ MI 2+
2	MS 4+ MI 0	27	Less than 3	6	1.8	10	Atrial fibrillation	RV LV	MS 4+ MI 2+
3	MS 4+ MI 1+	23	4	3	2.5	5	Atrial fibrillation	RV	MS 3+ MI 2+
4	MS 4+ MI 1+	20	4	7	1.8	9	Atrial fibrillation	RV LV	MS 3+ MI 2+

* Value over 3 mm. Hg indicates some mitral insufficiency.
† Value of 5 or more was taken to indicate severe mitral insufficiency.
‡ Value of 4 or more was taken to indicate predominant mitral insufficiency.

predicted, three were incorrect in degree only and in the other two cases evidence of insufficiency failed to show when it was later proved to be present (2+). When there was no involvement of the mitral valve (eleven cases), two showed the presence of some insufficiency which actually may have been present as a relative lesion. Both of these latter patients were in congestive failure.

Y Descent; Morrow Method: As has been indicated, the Morrow procedure[5] was quite successful in predicting the predominant lesion. In only three occasions of seventy-six, predominant insufficiency was indicated by this procedure when the lesion was not present at operation. These three cases included two cases with associated aortic stenosis in failure and one with failure alone. Of sixty-three cases showing severe mitral stenosis at operation (3–4+) fifty-nine showed a Morrow value in the range of 0–2, and four a value of 3–4. Out of thirteen cases showing a mild stenosis (1 or 2+), six were in the 0–2 and four in the 3–4 range. In cases of predominant insufficiency without significant stenosis, the Morrow method was less efficient, being correct seven times out of ten and wrong three. These three cases were also incorrectly predicted by the V/AC ratio method.

In the fourteen cases of combined mitral lesions, eleven proved to be predominant stenosis, and of these, ten were predicted correctly by the Morrow method with one being misdiagnosed as insufficiency. This patient was in congestive failure. In the two cases where the lesions were of equal degree, one was evaluated preoperatively as insufficiency and the other as stenosis by this criterion. The one case proven to be predominant insufficiency was correctly predicted by this method.

Predominant Mitral Insufficiency Diagnosed as Mitral Stenosis: Table IV shows the three patients eventually proved to have predominant mitral insufficiency who were incorrectly diagnosed by catheterization data prior to operation. In two of these, the electrocardiogram showed left ventricular hypertrophy and in the third it was not remarkable. X-ray examination showed definite left ventricular hypertrophy associated with hypertrophy of the right side in two cases. The mean atrial pressure did not show any great degree of variation from the average for the lesions involved, and was in itself of no help in making the final diagnosis.

Incorrect Evaluation of Mitral Insufficiency in Presence of Stenosis: Table V shows the data on

four patients sent to surgery with catheterization data indicative of severe stenosis with little or no mitral insufficiency. All four of these were found to have predominant stenosis, but with significant degrees of insufficiency. In three of these x-ray examination indicated significant enlargement of the left ventricle, while the electrocardiogram was nonspecific. Again, the mean atrial pressure in itself was of no diagnostic value. The Morrow determination in each case indicated predominant stenosis which was correct, but it should be noted that in the three cases with predominant insufficiency (Table IV), this method also indicated a value for stenosis.

Aortic Stenosis: While the catheterization data correctly predicted the degree of aortic stenosis in all seventeen cases sent to surgery, it should be pointed out that in an additional twenty patients not included in this series in whom the diagnosis of aortic stenosis was made clinically, the catheter study revealed that the lesion was not of sufficient magnitude to warrant operation.

Comments

Should it seem that the results presented here have shown the accuracy of the clinical examination alone in a rather unfavorable light, it should be remembered that this group of patients was selected for inclusion because they had left heart catheterization and therefore represent the more difficult diagnostic problems. Many other patients with acquired valvular disease were encountered during the same period whose clinical, x-ray and electrocardiographic examinations were considered sufficiently diagnostic in themselves, and these were sent to surgery without catheterization. Furthermore, the accuracy of the clinical examination is becoming increasingly greater as we obtain more experience in correlating our findings with the conditions revealed by surgery. The most frequently encountered clinical error was the tendency to interpret systolic murmurs at the apex as indicative of significant mitral insufficiency when in reality they might arise from a dynamically insignificant jet or from a referred murmur of tricuspid insufficiency or aortic stenosis.

The electrocardiogram was disappointing, although it occasionally gave a clue to the correct diagnosis when other data were in error. While not often actually misleading, the electrocardiogram in problem cases too often showed only nonspecific changes or failed to reveal the changes of hypertrophy that would have aided in the diagnosis. By contrast, the radiographic examination was quite helpful, particularly during the latter part of the series when newer methods of evaluating left ventricular hypertrophy and study of the pulmonary vasculature by laminography were employed. The principal problem in the x-ray evaluation is the extreme difficulty encountered in estimating lesser degrees of left ventricular hypertrophy in the presence of marked right ventricular enlargement.

Heart catheterization has been a considerable aid in establishing a definitive diagnosis prior to surgery. It is particularly helpful in stenotic lesions of either the mitral or aortic valve in which data may be obtained which will permit accurate evaluation of valvular area. Unfortunately, however, there is no completely successful method of evaluating the degree of mitral insufficiency in the presence of stenosis and under these conditions estimation of valvular area is inaccurate due to the inability to obtain the true cardiac output. Evaluation of the atrial pressure curve alone is not completely reliable in revealing the degree of mitral insufficiency, although many ingenious methods of analysis have been proposed which show a high degree of correlation. When one considers the extreme variations in atrial volume and distensibility, it is not difficult to see why any method of analysis depending upon pressure curves results in occasional failures. All methods of evaluation of the atrial curves were about equally effective, except for the Wells procedure of the corrected X descent, which did not give satisfactory results in our hands. The V/AC ratio, having the advantage of simplicity, probably gives as reliable results as any of the others, particularly in cases of sinus rhythm, while the fractional Morrow determination is especially well adapted for use in cases with atrial fibrillation. Fisher[2] points out that the analysis of the V wave height is unreliable in cases with relatively low (below 22) mean atrial pressure, although our failures did not show any particular correlation in this regard. Most of our difficulty occurred in cases where there was a high degree of left ventricular failure or an associated aortic valve lesion.

Summary

The results of the physical examination and

various accessory laboratory aids used in the diagnosis of valvular heart disease are compared to one another and evaluated in the light of the findings at operation and at autopsy. Physical examination alone is often inadequate for evaluation of the degree of stenosis or insufficiency which may be present in a mixed valve lesion and additional diagnostic aids, while often not supplying all of the necessary information, are helpful in arriving at a more precise quantitative diagnosis.

The various roentgenologic methods were found to be much more helpful than the electrocardiogram in all of the categories studied with the possible exception of quantitating the degree of aortic stenosis, in which the two methods were about equal.

Left heart catheterization was superior to both methods in evaluating cases of predominant mitral stenosis, both of the "pure" type and those with significant degrees of mitral insufficiency, but was less helpful in arriving at a precise quantitative diagnosis when mitral insufficiency was the predominating lesion. It is felt that a judicious use of all available diagnostic aids should be made in an attempt to give the surgeon as much information as possible prior to operation.

The opportunity that major heart surgery has afforded in making available a quick "check" on the findings of the physical examination has served to increase the accuracy of this medium considerably over the last few years. In addition, newer developments in the field of physiologic studies, including indicator dilution curves, selective angiocardiography and cinefluorography have added much to the ever increasing accuracy of preoperative diagnosis.

References

1. Fisher, D. L. The use of pressure recordings obtained at transthoracic left heart catheterization in the diagnosis of valvular heart disease. *J. Thoracic Surg.*, 30: 379, 1955.
2. Fisher, D. L. Catheterization of the left heart. In: Zimmerman, H. A. Intravascular Catheterization, Chap. 2, pp. 34–79. Springfield, Illinois, 1959. Charles C Thomas.
3. Allison, P. R. and Linden, R. J. Bronchoscopic approach for measuring pressures in the left auricle, pulmonary artery and aorta. *Lancet*, 268: 9, 1955.
4. Owen, S. G. and Wood, P. A new method for determining the degree or absence of mitral obstruction. An analysis of the diastolic part of indirect left atrial pressure tracings. *Brit. Heart J.*, 17: 41, 1955.
5. Morrow, A. G., Braunwald, E., Haller, J. A. and Sharp, E. H. Left atrial pressure pulse in mitral valve disease: A correlation of pressures obtained by transbronchial puncture with the valvular lesion. *Circulation*, 16: 399, 1955.
6. Wells, B. G. The diagnosis of mitral incompetence from left atrial pressure curves. *Brit. Heart J.*, 20: 321, 1958.
7. Wells, B. G. Personal communication.

Effect of Norepinephrine on the Phonocardiographic, Auscultatory and Hemodynamic Features of Congenital and Acquired Heart Disease*

GEORGE A. BOUSVAROS, M.D.

London, England

SIMPLE MANEUVERS such as breath-holding, changes in position, exercise, etc. have always been an integral part of careful auscultation of the heart. The increasing precision in diagnosis required in modern cardiology has stimulated the development of other methods useful in differential diagnosis, one of which is the administration of pressor agents. Phenylephrine was employed to accentuate faint diastolic murmurs in acute rheumatic carditis.[1] Norepinephrine was thought by Soloff and associates[2] to accomplish several effects: (1) distinction between innocent and organic murmurs; (2) differentiation of the systolic murmur of aortic stenosis from those of pulmonary stenosis and mitral regurgitation; and (3) uncovering of mitral insufficiency in patients thought to suffer from pure stenosis. These authors[3] also offered examples of the changes in intensity induced by norepinephrine of the systolic murmurs of mitral incompetence and ventricular septal defect (increased) and tricuspid insufficiency (unchanged). Accentuation of the systolic murmur of mitral regurgitation by means of norepinephrine was also observed by Perloff and Harvey.[4] Administration of mephentermine was advocated to produce the typical murmur in cases of patent ductus without a continuous murmur[5] and for intensification of various other murmurs.[6] Recently, the use of phenylephrine was reported to aid the distinction of pulmonary stenosis with intact ventricular septum from the tetralogy of Fallot.[7]

In the present study the effects of norepinephrine upon the auscultatory and phonocardiographic features in patients with organic heart disease are described. Observations on the hemodynamic changes induced by norepinephrine, made in order to assist interpretation of the phonocardiographic data, will also be reported.

MATERIAL AND METHODS

Seventy-nine patients were included in the investigation; their number is listed with the individual groups in the description of the results. The diagnosis was confirmed by surgery or autopsy in over two-thirds, and in the remainder after full cardiologic investigation, including catheterization and/or cardioangiography. Hemodynamic observations during administration of norepinephrine were made in twenty-three.

At catheterization the arterial and intracardiac pressures were recorded from the midthoracic level;† blood samples were analyzed for oxygen saturation with a spectrophotometer. Control oxygen consumption was determined by the Donald-Christie air-filled spirometer; during the infusion it was measured in only three patients. Values in these patients were the same as the control figure; in the remainder of the patients the control oxygen consumption was assumed unchanged, an assumption supported by data in the literature.[8,9]

After the diagnostic information had been assembled the catheter was reintroduced into the pulmonary artery and the control data were obtained. Norepinephrine, 8 μg. per ml. of saline, was then infused into an arm vein at a rate of 10 to 20 μg. per minute, which usually produced a 40 to 70 per cent elevation of systolic pressure above control levels.

† Electromanometers and photographic recorder by New Electronic Products, London, England.

* From the Cardiac Department, Guy's Hospital, London, England. Supported by a grant from the S. Achillopoulos Foundation, Volos, Greece.

When the pressure had been stable for one to two minutes the catheter was slowly withdrawn while phasic and mean pressures and blood samples were obtained; the infusion was then discontinued. In eight of the patients investigated during catheterization, 30–60 μg. of norepinephrine was injected through the intracardiac catheter with coincident continuous recording of the systemic and pulmonary arterial or right ventricular pressures. Cardiac output was not estimated during this abbreviated procedure, which usually lasted three to four minutes, as compared to ten to fifteen minutes for the complete one. The phonocardiogram was coincidently recorded in held expiration, with the high frequency setting and at the same attenuation, the microphone being placed in the optimal position for registering of the events under investigation.

In the patients not studied during catheterization, control blood pressure levels were measured by sphygmomanometer after the nature of the procedure and the possible side effects had been explained. Three to seven milliliters of the 8 μg. per ml. norepinephrine solution were then injected intravenously within forty-five to sixty seconds. The amount was predetermined empirically according to age, size of the patient and the resting blood pressure level, the latter in view of increased sensitivity to the drug in hypertensive subjects.[10] The pressure was checked immediately after the injection and at frequent intervals thereafter. Phonocardiograms were obtained in the supine or semirecumbent position with two microphones, consecutively to each pressure measurement; two recordings being inscribed at the peak pressor phase.

Results

Effect of Infusion of Norepinephrine on Blood Pressure and Heart Rhythm: With the single injection of norepinephrine, the maximal blood pressure elevation was attained at the end of the administration. The peak pressure was usually maintained for about twenty seconds and then declined, returning in three to four minutes to control levels.

Bradycardia was noted in all but eight of the patients; it was often less intense at the end of the injection and usually more pronounced at the second of the two recordings made during the peak pressor phase. Assessment of the phonocardiographic data was made from the first of these records, in order to avoid, as far as possible, the effects of bradycardia and ectopic beats. The increase of heart rate, on the other hand, was due to acceleration of the sinus node in five patients, nodal rhythm in two and increase of idioventricular rate in one who had congenital heart block.

Disorders of rhythm which appeared during the infusion were mainly ventricular and less commonly supraventricular ectopic beats. Nodal rhythm occurred in four patients. The incidence was higher in the noncatheterized patients (28 per cent), possibly due to the fast rate of infusion, and lower in those investigated during catheterization (17 per cent). One or more ventricular ectopic beats were commonly triggered in the latter patients as the catheter was withdrawn across the right ventricular outflow tract. These arrythmias have been ascribed to the increase of myocardial irritability caused by norepinephrine,[11] enhanced by bradycardia and the consequent diminution of the refractory period.[12] By contrast, reversal to sinus rhythm occurred in one patient who had a nodal rhythm prior to the infusion; norepinephrine has indeed been used to terminate supraventricular arrhythmias.[13]

Side Effects: Palpitations related to the ectopic beats, and a feeling of pressure and heaviness in the epigastrium and lower part of the thorax were the main side effects. Headache and dizziness were less frequent. Facial and digital pallor and increased depth of respiratory movements were also observed frequently. These effects were more frequent and of greater intensity but shorter duration in the patients who received the norepinephrine in a single injection. These effects were less common in those subjects given a continuous infusion, but when they occurred they lasted for the duration of the entire study.

Congenital Heart Disease

Pulmonary Stenosis: Eleven patients were studied (Table 1), in four of whom valvulotomy or infundibular resection had been performed one to ten years previously. Three patients were submitted to valvulotomy during the period of the study and the test was repeated three to ten weeks after the operation.

The pulmonary arterial pressure (systolic, diastolic and mean) was elevated in all seven cases in which it was measured. The right ventricular systolic and end diastolic pressures were augmented in seven patients and were impossible to determine in two, as the pressure tracing was obscured by numerous ectopic beats. The peak pulmonary systolic gradient increased in five cases by between 14 and 133 per cent. In two other cases, in which the pulmonary artery pressure was not determined during the infusion, the right ventricular systolic pressure exceeded the control figure by 55 and 34 mm.

TABLE I

Effect of Norepinephrine on the Hemodynamics and Phonocardiogram in Pulmonary Stenosis

Case No.	Sex, Age (yr.)		SP (mm. Hg)	PAP (mm. Hg)	RVP (mm. Hg)	PSG (mm. Hg)	SV (cc.)	HR (per min.)	SM	P_2	A_2-P_2 (sec.)	Comments
1	F, 45	C	137/84	29/10	115/11	86	76	70	5	+	...	
		N	217/106	33/12	183/15	150	72	60	16	+++	...	
2	M, 3	C	105/75	18/5	178/13	160	31	60	14	+	...	
		N	160/100	...	212/14	...	...	59	24	++	...	
3	M, 36	C	139/84	22/11	176/15	154	85	86	11	−	...	Preoperative test
		N	213/106	26/14	193/17	167	110	60	28	++	0.10	
		C	140/80	(16/4)	(32/15)	(16)	...	79	17	−	...	Postoperative test (5 weeks postvalvotomy)
		N	180/100	...	...	...	...	58	24	−	...	
4	F, 36	C	120/70	14/7	100/10	86	103	58	25	−	...	Preoperative test
		N	200/100	29/17	140/11	111	105	56	32	++	0.10	
		C	130/70	(32/24)	(44/20)	(12)	...	66	19	−	...	Five weeks after valvotomy
		N	200/100	...	...	...	...	47	30	−	...	
5	F, 15	C	111/68	14/7	109/10	95	...	94	22	+	0.11	Right to left shunt through PFO Arterial O_2 saturation 87%
		N	180/104	...	164/14	...	...	72	28	+++	0.08	
6	M, 40	C	100/70	32/24	144/16	112	...	75	11	−	...	Right to left shunt through PFO Arterial O_2 saturation 78%
		N	140/90	...	...	...	...	65	20	+	0.11	
7	F, 15	C	130/80	26/8	114/10	88	...	84	17	+	0.09	Preoperative test
		N	200/100	...	...	...	...	64	24	++	0.09	
		C	140/80	(34/18)	(100/19)	(62)	...	75	11	−	...	Test performed 4 weeks after valvotomy
		N	200/110	...	...	...	...	55	30	−	...	
8	M, 21	C	113/75	14/7	67/9	53	75	75	10	−	...	10 years after valvotomy
		N	190/110	26/10	142/17	116	65	62	40	++	0.05	
9	M, 10	C	120/58	29/10	35/10	6	63	52	23	+	0.07	3 years after valvotomy
		N	180/95	49/15	63/13	14	56	50	44	+++	0.06	
10	M, 10	C	120/80	25/11	52/12	27	36	94	13	−	...	One year after valvotomy
		N	200/116	38/13	...	...	41	69	18	++	0.05	
11	F, 19	C	113/80	21/10	54/11	33	55	83	5	−	...	10 years after valvotomy
		N	199/122	31/16	...	...	...	56	20	−	...	

Abbreviations as follows: C = control, N = during infusion of norepinephrine. SP = systemic pressure; PAP = pulmonary arterial pressure; RVP = right ventricular pressure; PSG = peak systolic gradient. SV = stroke volume; HR = heart rate; SM = systolic murmur; DM = diastolic murmur. P_2 = pulmonary component; A_2 = aortic component of the second sound. PF = pulmonary flow; SF = systemic flow; P:S = pulmonary to systemic (flow ratio). PFO = patent foramen ovale; MI = mitral insufficiency; ASD = atrial septal defect; VSD = ventricular septal defect; APVC = anomalous pulmonary venous connection; PDA = patent ductus arteriosus; A-P = aortopulmonary; PHT = pulmonary hypertension. Absence of right sided pressures in the N data denotes that the test was not performed during catheterization; in these patients hemodynamic data are taken from catheterization performed independently. Whenever pressures in one right heart location are quoted, this indicates that the abbreviated test was performed. Pressures within parentheses were measured on the operating table.

Hg. Elevation of pulmonary arterial pressure of such magnitude did not occur in any of the other patients, and it seems likely that the gradient was augmented in them as well.

Significant increase in the intensity of the systolic murmur was observed in all patients (Fig. 1), including the three studied in the postoperative period, without appreciable change in configuration or length. Ejection sounds, present in four patients, became louder under the influence of the drug (Fig. 1B). In most cases the pulmonary component of the second sound (P_2) was accentuated; it appeared for the first time on the records in five patients and became obvious in one which it had been doubtful (Fig. 1 and Table I). It failed to appear under the influence of norepinephrine in the patients studied in the early postoperative period and in one of the four who had been operated upon one to ten years before. The A_2-P_2 interval could be measured both before and during the test in three cases; it remained unchanged in one, and was shortened by 0.01 and 0.03 second in the others (Fig. 1A).

Tetralogy of Fallot: Cyanotic cases. The eight patients studied had an ejection systolic murmur with early crescendo typical for the tetralogy and a single second sound, with one

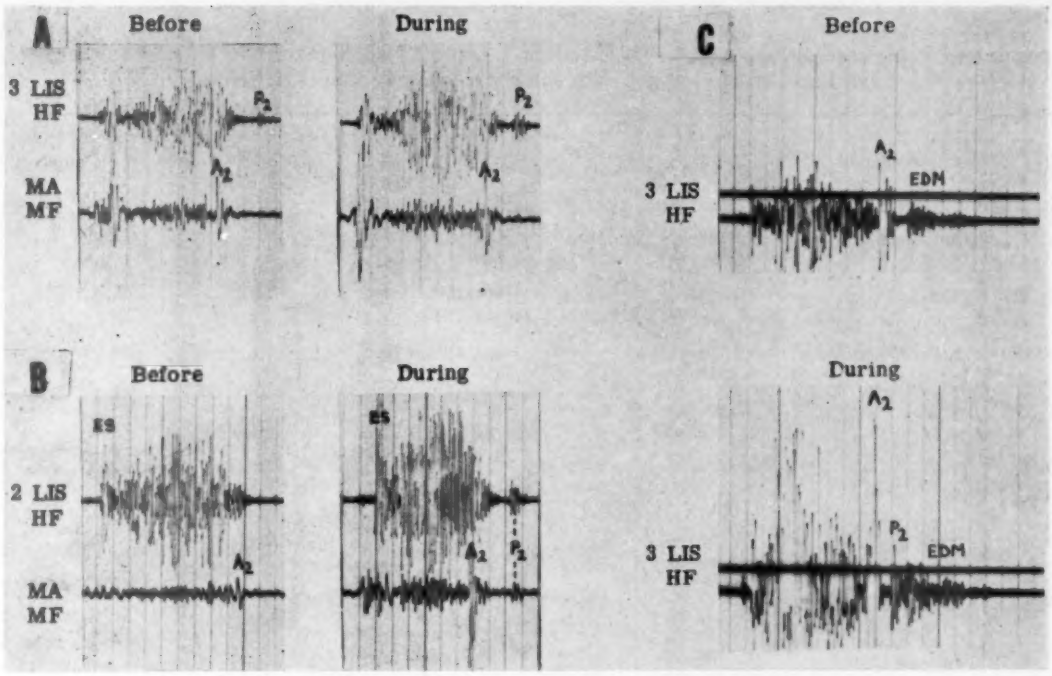


FIG. 1. Accentuation of the systolic murmur in three patients with pulmonary stenosis during injection of norepinephrine. Additional effects shown are: (A) louder P_2 and narrowing of the A_2-P_2 interval from 0.11 to 0.08 second; (B) accentuation of ejection sound and appearance of P_2, which is not seen in the control tracing. Note obvious shortening of the duration of systole. (C) increased loudness of diastolic murmur of pulmonary insufficiency and clear recording of P_2, which could not be separated from the diastolic murmur in the control tracing.

exception in whom P_2 was also recorded. *The murmur was accentuated in all patients.* It increased in duration by 0.04 second in one, and its crescendo moved toward midsystole in another. The pulmonary element of the second sound did not appear in any case during infusion of norepinephrine but became louder in the patient in whom it had been present prior to the test. In two of the five patients with subclavian to pulmonary arterial anastomoses the continuous murmur, easily audible, was intensified during the test. A faint continuous murmur in the third patient also became prominent with norepinephrine infusion; in the remaining two cases the murmur was inaudible and was not elicited with the test.

Acyanotic cases. In the nine patients of this subgroup the following changes were observed during administration of norepinephrine: (1) Accentuation of the systolic murmur without significant alteration in length; (2) shifting of the early crescendo of the murmur toward midsystole in two patients, but not in the other seven who had midsystolic crescendos; and (3) accentuation of P_2 in four instances and its appearance for the first time in two. P_2 failed to appear in two patients and could not be identified in three, probably being concealed within the coexisting murmur of pulmonary insufficiency. The A_2-P_2 interval (measured in three cases) remained unchanged. Data on the pressures and flows available in three patients are shown in Table II (Cases 23, 25, 26).

Ventricular Septal Defect: Four patients had a ventricular septal defect with pulmonary flow less than twice the systemic and normal or near normal pulmonary arterial pressure. No significant change in the shunts was detected during infusion of norepinephrine (Cases 29–31, Table II). The systolic murmur was accentuated without alteration in length in all four. A fifth patient (Case 32, Table II) had pulmonary hypertension and right to left shunt (Eisenmenger's complex). The auscultatory signs, consisting of ejection sound, short systolic murmur, loud P_2 and early diastolic murmur of pulmonary incompetence, were intensified under the influence of norepinephrine.

Atrial Septal Defect: The auscultatory signs in five cases of uncomplicated ostium secundum were not appreciably modified. Three patients with ostium primum defect showed accentuation of the accompanying mitral pansystolic murmurs. In another patient, who had a large

TABLE II

Hemodynamic and Phonocardiographic Observations of the Effect of Norepinephrine in Patients Investigated During Cardiac Catheterization, with the Exception of Pulmonary Stenosis

Case No.	Sex, Age (yr.)	Diagnosis	SP (mm. Hg)	PAP (mm. Hg)	RVP (mm. Hg)	PF (L./min.)	SF (L./min.)	HR (per min.)	Comments
23	F, 7	Acyanotic tetralogy	C 112/63	19/6	103/10	4.0	2.4	94	
			N 168/102	51/12	168/14	5.8	1.9	79	
25	F, 20	Acyanotic tetralogy	C 124/70	74/20	118/18	7.9	5.0	94	
			N 152/97	80/26	144/27	7.2	4.2	83	
26	F, 15	Acyanotic tetralogy	C 101/61	...	109/6	13.7	3.7	107	
			N 146/84	...	155/11	...	...	100	
29	F, 12	VSD	C 120/82	27/13	27/6	7.8	5.4	125	
			N 154/100	37/15	37/8	6.5	4.4	88	
30	F, 9	VSD	C 129/72	20/8	22/7	4.3	4.3	83	No shunt detected, but clinical evidence for VSD strong
			N 190/111	38/14	38/8	4.0	4.0	83	
31	F, 5	VSD	C 110/70	35/15	38/10	7.5	4.1	107	
			N 161/97	57/22	60/13	5.7	3.1	83	
32	F, 4	VSD, PHT	C 95/58	96/56	...	1.5	5.3	111	Arterial O_2 65%
			N 134/89	134/68	...	...	...	79	
33	F, 4	ASD (primum)	C 102/56	56/23	...	4.0	2.2	117	High wedge pressure (21 mm. Hg mean) due to MI
			N 131/101	74/42	...	...	...	125	
34	M, 14	ASD (primum)	C 101/64	26/10	26/7	20.0	7.2	70	
			N 145/100	39/14	...	...	...	60	
35	F, 42	ASD (secundum)	C 85/60	43/14	43/10	7.5	3.0	63	
			N 160/100	58/17	58/12	7.5	3.0	51	
36	F, 48	ASD-APVC-PHT	C 86/48	68/30	68/7	4.1	3.4	62	Bidirectional shunt mainly left to right
			N 142/72	104/46	104/10	...	...	71	Arterial O_2 86%
37	F, 4	PDA	C 126/61	100/61	...	...	...	100	P:S flow ratio 2.6
			N 168/127	168/127	...	...	...	107	
38	M, 16	A-P window	C 105/64	110/70	...	10.8	3.4	79	
			N 170/85	175/89	...	...	...	72	
39	F, 23	MS-PHT	C 109/73	...	128/20	2.5	2.5	88	Functional tricuspid insufficiency with systolic murmur which disappeared with nodal rhythm
			N 205/89	...	196/19	...	...	40	

Abbreviations and explanations as in Table I.

defect with subtotal anomalous pulmonary venous connection and pulmonary hypertension, there was a loud systolic murmur of tricuspid insufficiency which was moderately intensified (Fig. 2). Hemodynamic data in four cases are given in Table II (Cases 33–36).

Aortopulmonary Communications: One patient with patent ductus arteriosus, large left to right shunt and pulmonary hypertension (Case 37, Table II) had a systolic murmur at the second and third left interspaces and an apical flow murmur. With norepinephrine infusion the pulmonary artery systolic pressure was augmented more than the systemic and became equal to it; the systolic murmur disappeared (Fig. 3). The second patient (Case 38, Table II) had an aortopulmonary window with high pulmonary arterial pressure, low pulmonary vascular resistance and substantial left to right shunt, evidenced clinically by an apical flow murmur. In addition to this, he had a short pulmonary systolic murmur, ejection sound and early diastolic murmur of pulmonary insufficiency, which were accentuated with administration of norepinephrine. The third patient had persistent truncus arteriosus and the sounds and murmurs, similar to those of the previous case, were also accentuated.

The effect of norepinephrine on the pulmonary arterial and systemic pressures in the first two patients is interesting in comparison to that in the patient with Eisenmenger's complex. In the former the diastolic pressures in the two vascular circuits remained identical, or nearly so, suggesting that the two sides were in communication during diastole. In the latter

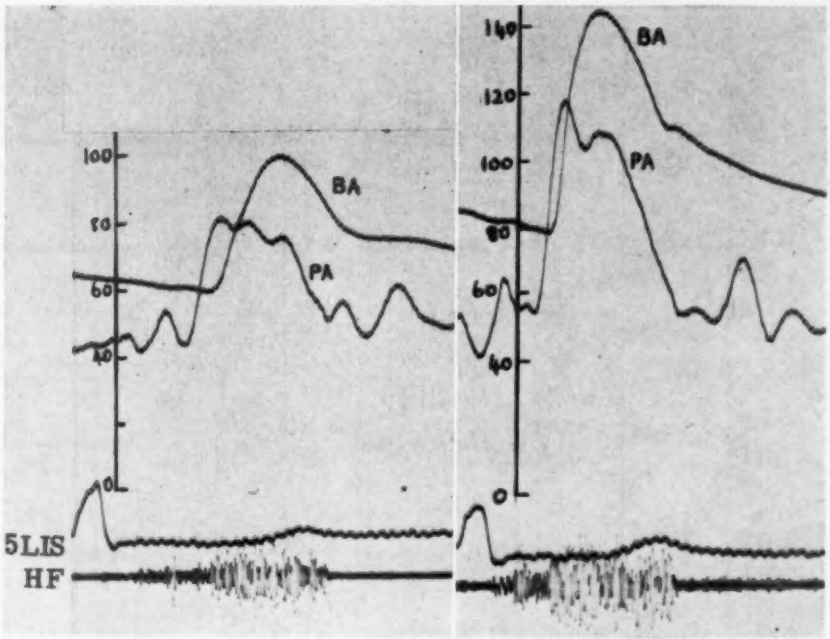


FIG. 2. Simultaneous phonocardiogram and pulmonary artery pressure tracing in a patient with atrial septal defect, anomalous pulmonary venous connection and pulmonary hypertension, demonstrating increased intensity of the systolic murmur of tricuspid insufficiency and elevation of pulmonary arterial pressure before (A) and during (B) injection of norepinephrine.

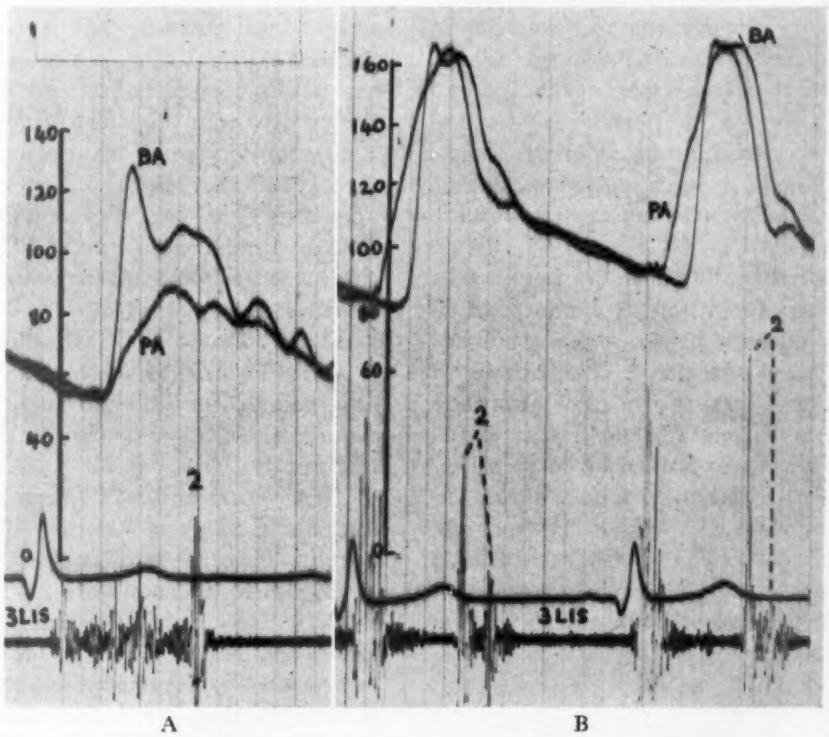


FIG. 3. Brachial and pulmonary artery pressures in a patient with patent ductus arteriosus. Note disappearance of the systolic murmur during (B) norepinephrine infusion and proportionately greater rise of pulmonary arterial pressure; the pressures are now equal. (A, before infusion; B, after.)

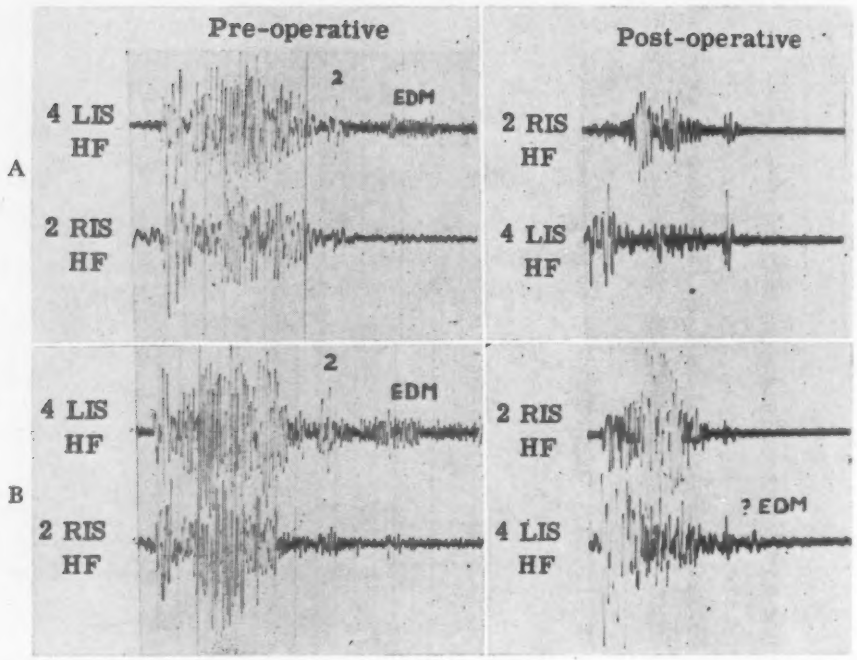


FIG. 4. Pre- and postoperative tracing in a case of aortic stenosis and insufficiency. Intensification of both murmurs following norepinephrine infusion occurs in the preoperative test. Postoperatively, the diastolic murmur is faintly recorded, even with norepinephrine, indicating diminution of the regurgitation. (A, before; B, during infusion.)

only the systolic pressures remained identical, the systemic diastolic exceeding the pulmonary during the hypertensive phase (Table II).

Primary Pulmonary Hypertension: One patient with primary pulmonary hypertension was investigated. The auscultatory features consisted of a loud P_2 and a right ventricular filling sound, both of which were accentuated with norepinephrine.

Pulmonary Insufficiency: In two patients early diastolic murmurs of pulmonary incompetence secondary to pulmonary hypertension were accentuated with norepinephrine coincident to further rise of pulmonary arterial pressure. In six other cases pulmonary insufficiency was not associated with pulmonary hypertension, being secondary to pulmonary valvotomy in five and congenital in the sixth. These early diastolic murmurs were also intensified and thereby became clearly recorded in three patients, in whom they previously had been soft or dubious (Fig. 1C).

ACQUIRED HEART DISEASE

Mitral and Tricuspid Insufficiency: There were nine patients with mitral regurgitation, pure in four and associated with mitral stenosis in five. Three additional patients had mitral incompetence as a component of ostium primum atrial septal defect. *The systolic murmurs became louder in every instance* and longer, extending into early systole in three patients with pure insufficiency in whom the murmurs were late systolic.

Tricuspid systolic murmurs encountered in three patients were also intensified with norepinephrine (Fig. 2); the hemodynamic changes in two appear in Table II (Cases 36 and 39). After a brief period of accentuation the systolic murmur disappeared in one of them, coincident to development of nodal rhythm.

Mitral and Tricuspid Stenosis: No change was observed in the diastolic murmur of eleven patients with mitral stenosis and two with tricuspid stenosis.

Aortic Stenosis and Insufficiency: Seventeen patients had aortic valvular disease, this being pure in eleven (four of them were probably congenital); four cases were restudied three to six weeks after aortic valvotomy. *The ejection systolic murmur of aortic stenosis was accentuated in every instance* without appreciable change in shape or length (Fig. 4). The aortic second sound was intensified as well as any pre-existing aortic diastolic murmur. The latter became obvious in the phonocardiogram and was heard clinically for the first time in three patients. Ven-

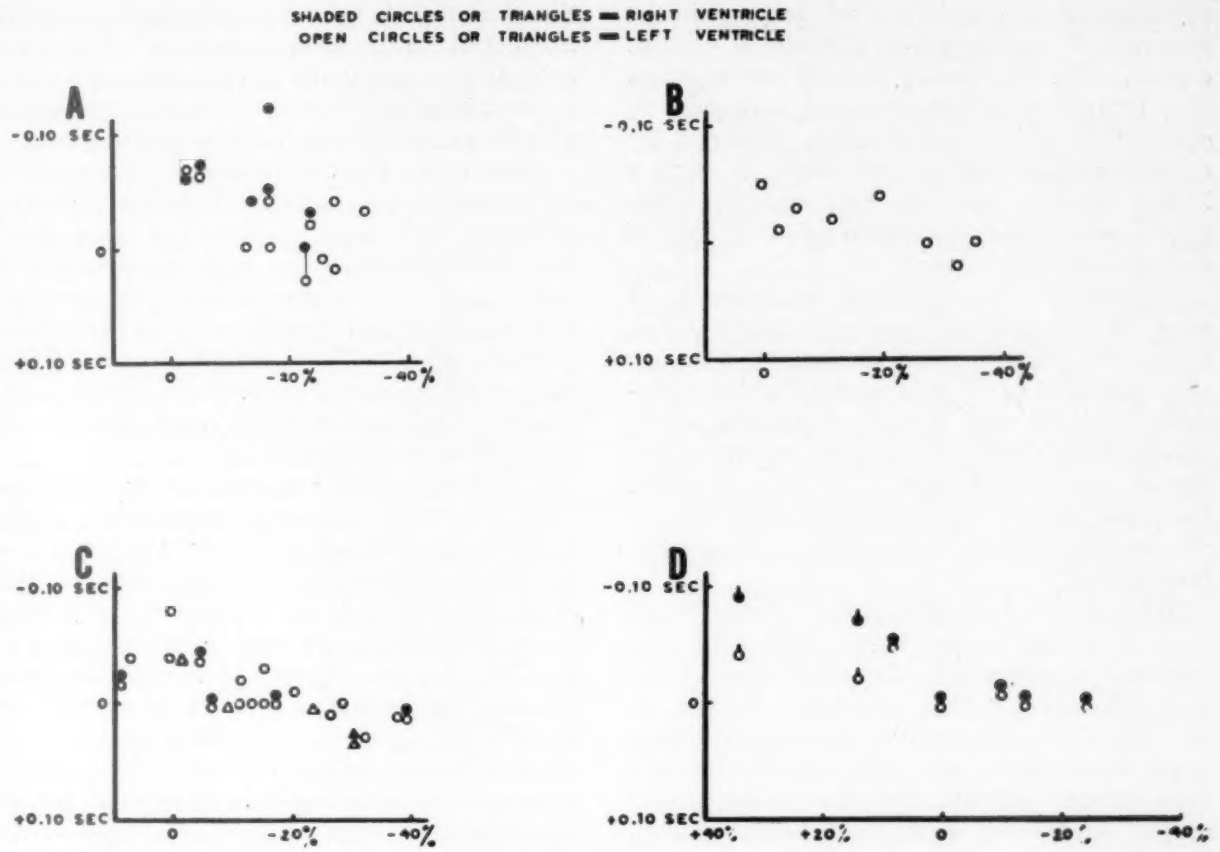


FIG. 5. Per cent changes in duration of left and right ventricular systole in hundredths of a second (ordinate) related to the per cent changes of heart rate (abscissa) in patients with pulmonary stenosis (section A), aortic stenosis (section B), tetralogy and ventricular septal defect (section C; circles = Fallot, triangles = ventricular septal defect) and atrial septal defect (section D). The changes are equal in both ventricles, with four exceptions in which right ventricular systole was abbreviated more than the left. Three of the four exceptions had pulmonary stenosis and the two values are connected with a line in each case. In the fourth patient, who had atrial septal defect and pulmonary hypertension, right ventricular systole was abbreviated more than the left with two different heart rates (respective values marked with rods). Explanation of this phenomenon is not available, but the presence of right ventricular hypertrophy as a common factor is noteworthy.

tricular filling sounds were accentuated in two cases and appeared *de novo* in three; atrial sounds increased in two patients, decreased in two, and showed no change in three.

Effect of Norepinephrine on the Duration of Systole: The duration of systole in each ventricle was determined from the peak of the R wave of the electrocardiogram (being more accurate to identify than the first sound) to the respective component of the second sound; in a few it was measured from the pressure tracings, as duration of ejection. Difficulty in accurate identification of each component of the second sound allowed measurements in just over half the patients for left ventricular systole and in a minority for the right, whenever wide splitting of the second sound permitted unequivocal recognition of P_2. Changes in duration of systole were plotted against changes in heart rate (Fig. 5). Good relationship between these parameters is seen: with increased rate systole became invariably shorter, while it was usually prolonged with bradycardia. Abbreviation of systole or no change was, however, noted in a few patients despite reduction in heart rate (Fig. 1B). The relationship suggests that in addition to the effect of heart rate there was a tendency for abbreviation of systole, prevented at times by marked bradycardia. As changes of isometric contraction and electromechanical interval with norepinephrine are probably small and in the same direction, these observations probably apply to ejection as well.

COMMENTS

HEMODYNAMIC EFFECTS OF NOREPINEPHRINE

That norepinephrine raises systemic resistance in man[14] was confirmed in the present study by

considerable increase in systemic pressure in the presence of unchanged or diminished cardiac output. The pulmonary arterial pressure was also elevated, whenever measured, as in previous studies.[14,15] Additional changes produced by norepinephrine will be discussed in greater length, as they seem to have caused, singly or in combination, the accentuation of most of the murmurs investigated.

Bradycardia: The observed bradycardia in most of the patients was probably a reflex to the elevation of blood pressure.[16] The rise of systemic pressure, as reported,[17] usually preceded the reduction of rate; assessment of the phonocardiographic data with minor interference from bradycardia was thus possible. Its importance is, however, evident by further accentuation of murmurs with subsequently lower rates.

Abbreviation of Ventricular Systole: This occurred in most patients, except for those with pronounced bradycardia. In the latter cases, although ejection was prolonged in the individual cycle, the ejection period per minute, being the product of the former and the reduced rate, was abbreviated. Expulsion of the cardiac output in shorter time most likely resulted in higher velocity of ejection; this factor appears by far the most important in the causation of greater amplitude of the murmurs.

The tendency for shorter ventricular systole under the influence of norepinephrine was shown to be independent of the heart rate and, by extension, of the stroke volume which is directly related to the rate. Its cause seems, therefore, to reside in either or both additional variables introduced by the test; namely, the increase of pressure in the respective vascular compartment and the direct effect of the catecholamine upon the ventricular myocardium. Animal experiments on the consequences of aortic pressure augmentation on the length of left ventricular systole have given conflicting results;[18,19] testing of the various parameters independently in an isolated heart preparation showed that moderate elevation of systemic pressure did not affect the duration of ejection, which was abbreviated by direct myocardial action of norepinephrine, amongst other sympathomimetic amines.[20] In the present series these effects could not be studied separately. However, the major resistance to ventricular outflow in the patients with aortic and pulmonary stenosis was offered by the obstruction and not by the corresponding vascular circuit; therefore, rise of vascular pressure could not have influenced the duration of ejection. Therefore, one has to accept that a direct myocardial effect of norepinephrine was mainly or solely responsible for the abbreviation of ventricular systole.

Changes in Pressure Gradients: Increase of *mitral regurgitation* under the influence of norepinephrine has been metered in animals[21,22] and shown indirectly in man by elevation of mean and V pressure in the left atrium.[23] Rise of systolic and diastolic pressure in the right ventricle is also likely to produce increased *tricuspid regurgitation*. Accentuation of the murmurs of mitral and tricuspid insufficiency probably occurs on this basis.

Augmentation of amplitude of the early diastolic murmurs in *aortic and pulmonary insufficiency* strongly suggested increased regurgitation at the corresponding semilunar valves; this may be considered a reasonable conclusion, as norepinephrine elevates diastolic pressure in both circuits. Very interesting, therefore, although unconvincing, is a recent article[24] reporting reduction of aortic regurgitation as a result of norepinephrine administration.

In patients with *ventricular septal defect* greater elevation of pressure in the left than in the right ventricle resulted in a higher gradient between the two chambers; one might thereby anticipate increase of left to right shunt with norepinephrine such as was observed in one patient by Fowler.[25] The shunts were, however, not appreciably altered in four patients and in two others with pulmonary stenosis and interventricular communication. This may be explained by increase of resistance of shunt flow offered by the defect or even by actual reduction of its size due to the inotropic action of norepinephrine on the septal musculature. This is probably not the only mechanism, for similar reduction in the absolute magnitude of left to right shunt with norepinephrine has been observed in experimental extracardiac communication between the two ventricles.[26]

Increase of the gradient in *pulmonary stenosis* under the influence of norepinephrine documented in five patients in this series is probably being described for the first time in man, but has been observed in dogs across experimental constriction of the pulmonary artery.[27] Variation in the resistive force opposing outflow in cases of aortic stenosis was postulated by Breall and Shaffer[28] for explanation of the changes in the gradient occurring with arrhythmias. Significant impairment of the opening of the valvu-

lar dome by constriction of its ring seems, however, rather unlikely; appearance or enhancement of muscular infundibular obstruction, on the other hand, is possible in view of the inotropic properties of norepinephrine. This mechanism might be responsible for the inordinate increment in gradient in Case 8 (Table 1) in which occurrence of muscular infundibular obstruction had been observed during the preliminary diagnostic catheterization.[29] Unfortunately, no record was made of the actual withdrawal across the pulmonary valve and infundibular region, and therefore no objective evidence[30] of the location of the increased gradient during administration of norepinephrine is available in this case. Occurrence of muscular infundibular obstruction could be definitely excluded in the other four patients.

Augmentation of pulmonary flow which is capable of increasing the gradient, as in the canine experiments,[27] was not encountered in any patient. Thus, by elimination of the previous two, one arrives at the following causative factors: (1) abbreviation of the ejection period per minute, to which the square root of the gradient is inversely proportional,[31] and (2) increase in central volume,[24,32] which is capable of elevating intracardiac pressures,[33] conceivably more so proximal to an obstruction.

Myocardial Stimulation: Augmentation of contractile force, due to the inotropic action of norepinephrine,[34] may result in higher velocity of ejection and consequently greater intensity of systolic murmurs. From the hemodynamic aspect, it is doubtful whether this effect of norepinephrine had expression other than the abbreviation of systole and perhaps the increase of gradient.

SYSTOLIC MURMURS

Administration of norepinephrine resulted in accentuation of systolic murmurs without occurrence of specific features which would enable distinction between any two of them. The claim that *mitral insufficiency* may be differentiated from tricuspid insufficiency[3] could not be substantiated. The differentiation of mitral incompetence and ventricular septal defect, which may be difficult in young persons, was also not aided. Intensification of subliminal mitral systolic murmurs was also not observed in this series; demonstration of so slight mitral regurgitation is probably of no significance because it would not modify the indications for surgery. The constant accentuation of the systolic murmur of *aortic stenosis*, without change in configuration, is also not in agreement with the reported attenuation in three of five patients.[2]

Pulmonary stenotic murmurs were accentuated without emergence of features, as claimed for phenylephrine,[7] which would allow differentiation of pure pulmonary stenosis from Fallot's tetralogy. Thus, lengthening of the short systolic murmur of cyanotic tetralogy was not observed (with one exception). The prolongation of the systolic murmur obtained by Vogelpoel et al.[7] with phenylephrine was considerable but of doubtful value, since, in the presence of a short murmur, the diagnosis of the tetralogy is seldom in doubt. The difficulty lies in the differentiation of the acyanotic type, which presents long systolic murmurs; in this direction norepinephrine provided no help.

Attenuation of a systolic murmur was noted in two patients. Almost complete disappearance of a tricuspid systolic murmur occurred in one, as a result of development of nodal rhythm. The second case was one of patent ductus, in which attenuation of the systolic murmur was observed although its substitution by a continuous murmur had been anticipated from the report of Crevasse and Logue.[5] Disappearance of the murmur, assuming that it was generated at the duct, strongly suggests interruption of the shunt, also evidenced by the obliteration of the difference in pressure between the aorta and the pulmonary artery. This isolated observation carries interesting hemodynamic implications, for it suggests that norepinephrine produced elevation of pulmonary vascular resistance. It also raises the question of what extent this was the result of local injection, the pulmonary arterioles being thus subject to higher concentration of the amine.

DIASTOLIC MURMURS

No significant alteration of mitral or tricuspid stenotic and flow murmurs was demonstrated. Early diastolic murmurs of pulmonary or aortic insufficiency were, on the other hand, considerably accentuated. In the case of aortic regurgitation perception of a hitherto unrecognized diastolic murmur cannot suggest more than trivial reflux and would not influence the prognosis or the indications for surgery (Fig. 4). In pulmonary insufficiency not secondary to pulmonary hypertension, on the other hand, the low-pitched early diastolic murmur may be confused, if faint, with a third

sound or a muffled pulmonary component; administration of norepinephrine usually clarifies such cases by accentuating the faint auscultatory findings.

CONTINUOUS MURMURS

A previously inaudible continuous murmur was heard after administration of norepinephrine in a patient who had a subclavian-pulmonary artery anastomosis performed in 1950 and whose condition deteriorated after initial improvement. The patient unfortunately declined further investigation, which might have shown whether administration of norepinephrine may result in distinction between anatomic obliteration of the anastomosis or interruption of flow due to development of pulmonary hypertension.[35]

HEART SOUNDS

Behavior of P_2 in Pulmonary Stenosis and Postvalvotomy: Changes of the first heart sound were on the whole unremarkable. Accentuation of ejection clicks, third sounds, aortic components and variable behavior of atrial sounds had no practical significance. Of more value was the accentuation or appearance *de novo* of P_2 in pulmonary stenosis, associated with and probably caused by the rise of pulmonary arterial pressure. Emergence of P_2 with the aid of norepinephrine allows accurate measurement of the A_2-P_2 interval, which reflects the severity of the stenosis.[36,37] Help is particularly required after pulmonary valvotomy, whereby P_2 is often not recorded, although the stenosis has been relieved. Registration of P_2 close to A_2 and a narrow interval will indicate such a state; whereas, in case of inadequate valvotomy, P_2 will be inscribed more distally, according to the severity of the residual obstruction. Burchell[38] has recently pointed out the difficulty in the clinical diagnosis of pulmonary stenosis in addition to ventricular septal defect when the two components of the second sound cannot be distinguished. Accentuation of P_2 with norepinephrine may be of help in this situation.

P_2 in Pulmonary Stenosis vs. Tetralogy: The differential diagnosis between pulmonary stenosis and Fallot's tetralogy was not aided by the behavior of P_2 since this component of the second sound was accentuated in both. Narrowing in the splitting occurred in only one of the three patients who, out of a total of eleven cases of pure pulmonary stenosis, had both components identified. The significant diminution in the A_2-P_2 interval, reported to have occurred in pure pulmonary stenosis with the use of phenylephrine,[7] is at variance with the present findings. Difference in the pharmacologic properties of the two drugs does not provide an adequate explanation for the discrepancy. Inspection of Figure 4 of that publication[7] gives rise to some doubt as to the accuracy of the quoted A_2-P_2 interval, since A_2 was defined within the late crescendo of the systolic murmur, without a simultaneous apical phonocardiogram or carotid sphygmogram. Furthermore, the sound labeled as A_2 in the second from the left tracing in the same illustration is probably P_2, the aortic component being obscured by the murmur. This record appears to show accentuation of P_2, although the authors state the contrary.

Conclusions

It is evident that little aid may be derived from the clinical use of norepinephrine because of the uniform accentuation of nearly all systolic and early diastolic murmurs. Two exceptions were encountered; they are interesting from a hemodynamic point of view but were of no diagnostic value. The disappointing results are probably related to the elevation of pressure in both systemic and pulmonary circulations resulting in no difference in the behavior of the murmurs on the two sides: furthermore, the rise of systemic resistance did not prevent intensification of aortic stenotic murmurs, which could not be distinguished from mitral regurgitant murmurs on this basis. On the other hand, helpful information was sometimes obtained by accentuation of doubtful signs, such as diastolic murmurs or the pulmonary component of the second sound.

Although application of norepinephrine does not seem helpful at the bedside, its administration in the course of cardiac catheterization seems more promising. Distinction between the tetralogy of Fallot and pure pulmonary stenosis is feasible by recording a similar rise of systemic and right ventricular pressure in the former, whereas the pressures separate in the latter. The use of norepinephrine for this purpose, already mentioned in the literature,[39,40] has been in our hands more reliable than the familiar exercise test which is cumbersome, time-consuming and exhausting for a disabled patient. As shown by the present work, norepinephrine may further effect discrimination between various forms of pulmonary hypertension. Failure of the systemic and pul-

monary diastolic pressures to diverge during the test would favor aortopulmonary communication rather than one at the ventricular level where only the systolic pressures would remain the same. Separation of both systolic and diastolic pressures in the systemic and pulmonary circulations would suggest the absence of any shunt or one at the atrial level. Simultaneous determination of flow would probably increase the amount of information thus obtained.

Summary

The effect of intravenous administration of norepinephrine on the auscultatory and phonocardiographic features was studied in seventy-nine patients with congenital or acquired heart disease. The investigation was carried out during cardiac catheterization in twenty-three, making possible the observation of the hemodynamic consequences of the infusion.

During the pressor response, accentuation of systolic and early diastolic and continuous murmurs was seen, with only rare exceptions; middiastolic murmurs were not altered. With reference to the cardiac sounds, increased intensity of P_2 was the most significant finding. This allowed determination of the degree of splitting of the second sound which is of importance in the evaluation of severity in pure pulmonary stenosis, particularly after valvotomy. It is mainly by intensifying faint signs, which thus become easy to identify, that administration of norepinephrine may offer auxiliary information helpful at the bedside and in phonocardiography.

More information regarding the presence and localization of abnormal communications was derived by observing the behavior of the systemic and right ventricular or pulmonary arterial pressures under the influence of norepinephrine.

Acknowledgment

I am most indebted to Sir Russel Brock, Dr. Charles G. Baker, Mr. D. N. Ross and Dr. D. C. Deuchar for permission to study their patients, and to Drs. D. C. Deuchar, A. M. Johnson and C. A. MacLeod for guidance and supervision during the cardiac catheterization tests. I am also most appreciative of the invaluable technical assistance by Mr. F. H. Muir.

References

1. Besterman, E. M. M. The use of phenylephrine to aid auscultation of early rheumatic diastolic murmurs. *Brit. Med. J.*, 2: 205, 1951.
2. Soloff, L. A., Wilson, M. F., Winters, W. L. and Zatuchni, J. Responses of cardiac murmurs to norepinephrine. *Circulation*, 18: 783, 1958.
3. Soloff, L. A., Cortes, F., Winters, W. L. and Zatuchni, J. The pansystolic regurgitant murmur: a simple method of identifying its anatomic source. *Am. J. M. Sc.*, 237: 745, 1959.
4. Perloff, J. K. and Harvey, W. P. Auscultatory and phonocardiographic studies of pure mitral insufficiency. *Circulation*, 18: 766, 1958.
5. Crevasse, L. and Logue, B. Atypical patent ductus: the use of a vasopressor agent in diagnosis. *Circulation*, 19: 332, 1959.
6. Crevasse, L. The use of a vasopressor agent as a diagnostic aid in auscultation. *Am. Heart J.*, 58: 821, 1959.
7. Vogelpoel, L., Schrire, V., Nellen, M. and Swanepoel, A. The use of phenylephrine in the differentiation of Fallot's tetralogy from pulmonary stenosis with intact ventricular septum. *Am. Heart J.*, 59: 489, 1960.
8. Reale, A., Kappert, A., Skogbard, C. H. and Sutton, G. C. The effect of l-noradrenaline on the oxygen consumption of human beings. *Acta physiol. scandinav.*, 20: 153, 1950.
9. Whelan, R. F. and Young, I. M. The effect of adrenaline and noradrenaline infusion on respiration in a man. *Brit. J. Pharmacol.*, 8: 98, 1953.
10. Doyle, A. E. and Black, H. Reactivity to pressor agents in hypertension. *Circulation*, 12: 974, 1955.
11. Zoll, P. M., Linenthal, A. J., Gilson, W., Paul, M. H. and Norman, L. R. Intravenous drug therapy of Stokes-Adams disease. Effects of sympathomimetic amines on ventricular rhythmicity and atrioventricular conduction. *Circulation*, 17: 325, 1958.
12. Lepeschkin, E., Marchet, A., Schroeder, G., Wagner, R., de Paula E Silva, P. and Raab, W. Effect of norepinephrine and epinephrine on the electrocardiogram of 100 normal subjects. *Am. J. Cardiol.*, 5: 594, 1960.
13. McGinn, J. T. and Schluger, J. Levarterenol bitartrate (Levophed) in the treatment of cardiac arrhythmias. *Am. Heart J.*, 50: 625, 1955.
14. Goldenberg, M., Pines, K. L., Baldwin, E. de F., Greene, D. G. and Roh, C. E. The hemodynamic response of man to norepinephrine and epinephrine and its relation to the problem of hypertension. *Am. J. Med.*, 5: 792, 1948.
15. Fowler, N. O., Westcott, R. N., Scott, R. C. and McGuire, J. The effect of norepinephrine upon pulmonary arteriolar resistance in man. *J. Clin. Invest.*, 30: 517, 1951.
16. Barcroft, H. and Konzett, H. Action of noradrenaline and adrenaline on human heart rate. *Lancet*, 1: 147, 1949.
17. Barnett, A. J., Blacket, R. B., Depoorter, A. E., Sanderson, P. D. and Wilson, G. M. The action of noradrenaline in man and its relation to pheochromocytoma and hypertension. *Clin. Sc.*, 9: 151, 1950.
18. Wiggers, C. J. Studies on the consecutive phases of the cardiac cycle. II. The laws governing the relative duration of ventricular systole and diastole. *Am. J. Physiol.*, 56: 439, 1921.
19. Remington, J. W., Hamilton, W. F. and Ahlquist, R. P. Interrelation between the length of systole, stroke volume and left ventricular work in the dog. *Am. J. Physiol.*, 154: 6, 1948.
20. Braunwald, E., Sarnoff, S. J. and Stainsby,

W. N. Determinants of duration and mean rate of ventricular ejection. *Circulation Res.*, 6: 319, 1958.

21. Braunwald, E., Welch, G. H., Jr. and Sarnoff, S. J. Hemodynamics of quantitatively varied experimental mitral regurgitation. *Circulation Res.*, 5: 539, 1957.
22. Ross, J., Jr., Cooper, T. and Lombardo, C. R. Hemodynamic observations in experimental mitral regurgitation. *Surgery*, 47: 795, 1960.
23. Braunwald, E., Welch, G. H., Jr. and Morrow, A. G. The effect of acutely increased systemic resistance on the left atrial pressure pulse: A method for the clinical detection of mitral insufficiency. *J. Clin. Invest.*, 37: 35, 1958.
24. Regan, T. J., DeFazio, V., Binak, K. and Hellems, H. K. Norepinephrine induced pulmonary congestion in patients with aortic valve regurgitation. *J. Clin. Invest.*, 38: 1564, 1959.
25. Fowler, N. O. Physiologic studies of drugs in human pulmonary hypertension. In: Pulmonary Circulation. New York and London, 1959. Grune & Stratton.
26. Siegel, J. H. A study of the mechanisms of cardiovascular adaptation to an acute ventricular septal defect. *J. Thoracic & Cardiovasc. Surg.*, 41: 523, 1961.
27. Fowler, N. O., Duchesne, E. R. and Franch, R. H. Hemodynamic effects of levarterenol infusion during induced pulmonary stenosis. *J. Pharmacol. & Exper. Ther.*, 120: 115, 1957.
28. Breall, W. S. and Shaffer, A. B. Effect of heart irregularity on left ventricular and arterial peak systolic pressures in aortic stenosis. *Circulation*, 20: 6, 1959.
29. Johnson, A. M. Norepinephrine and cyanotic attack in Fallot's tetralogy. *Brit. Heart J.*, 23: 197, 1961.
30. Johnson, A. M. Functional infundibular stenosis: its differentiation from structural stenosis and its importance in atrial septal defect. *Guy's Hosp. Rep.*, 108: 373, 1959.
31. Gorlin, R. and Gorlin, S. G. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. *Am. Heart J.*, 41: 1, 1951.
32. Shadle, O. W., Moore, J. C. and Billig, D. M. Effect of l-arterenol infusion on central blood volume in the dog. *Circulation Res.*, 3: 385, 1955.
33. Rushmer, R. F. Cardiovascular Dynamics, p. 26. Philadelphia and London, 1961. W. B. Saunders & Co.
34. Bloodwell, R. D., Goldberg, L. I., Braunwald, E., Gilbert, J. W., Ross, J., Jr. and Morrow, A. G. Myocardial contractility in man: the acute effects of digitalis, sympathomimetic amines and anoxic cardiac arrest. *Surg. Forum*, 10: 539, 1960.
35. Ross, R. S., Taussig, H. B. and Evans, M. H. Late hemodynamic complications of anastomotic surgery for treatment of the tetralogy of Fallot. *Circulation*, 18: 553, 1958.
36. Leatham, A. and Weitzman, D. Auscultatory and phonocardiographic signs of pulmonary stenosis. *Brit. Heart J.*, 19: 303, 1957.
37. Dimond, E. G. and Benchimol, A. Phonocardiography in pulmonary stenosis: special correlation between hemodynamics and phonocardiographic findings. *Ann. Int. Med.*, 52: 145, 1960.
38. Burchell, H. B. Bedside cardiac diagnosis (are history, physical examination, and clinical judgement outmoded?). *Postgrad. Med.*, 28: 1, 1960.
39. Turchetti, A. Condorelli's test for the diagnosis of ventricular septal defect. Abstract of scientific papers of 2nd World Congress of Cardiology, Washington, D. C., 1954.
40. Loogen, F. Diagnostic der angeborenen Pulmonalstenose. *Thoraxchirurgie*, 7: 212, 1959.

Hemodynamic Effects of Amyl Nitrite and Phenylephrine on the Normal Human Circulation and Their Relation to Changes in Cardiac Murmurs*

WALTER BECK, M.SC., M.R.C.P., VELVA SCHRIRE, PH.D., F.R.C.P.E., LOUIS VOGELPOEL, M.D., M.R.C.P., MAURICE NELLEN, M.D., M.R.C.P. *and* ANDRÉ SWANEPOEL, M.B., M.R.C.P.

Cape Town, South Africa

THE DIAGNOSTIC value of amyl nitrite and phenylephrine in differentiating cardiac murmurs has been described in previous communications from this clinic[1–3] and elsewhere.[4,5] In general, left-sided regurgitant murmurs (e.g., the murmurs of ventricular septal defect, mitral incompetence and patent ductus arteriosus) are softened by amyl nitrite and markedly accentuated by phenylephrine. These effects were attributed to the marked fall and rise in systemic blood pressure brought about by amyl nitrite and phenylephrine, respectively. On the other hand, ejection systolic murmurs (with the notable exception of Fallot's tetralogy) and all pulmonary and tricuspid murmurs were noted to be accentuated by amyl nitrite and inconstantly affected by phenylephrine.

These effects of amyl nitrite could be explained only by an increase in the velocity of ejection and an increased venous return to the heart. In support of an increased venous return after administration of amyl nitrite was the indirect evidence of a striking rise in right ventricular pressure which occurred in cases of pulmonary stenosis with intact ventricular septum following inhalation of amyl nitrite.[1]

On reviewing the literature it became evident that variable effects on cardiac output and venous return have been ascribed to the nitrates and nitrites. Lindhard[6] noted a significant increase in cardiac output of 23 per cent after inhalation of amyl nitrite. Weiss and Ellis[7] and Starr et al.[8] noted insignificant changes in cardiac output following administration of sodium nitrite. Lauber and Brauch,[9] calculating cardiac output from the pulse curve, first noted an increase then a fall in output after administration of nitroglycerine. Brandt et al.,[10] using the ballistocardiogram and roentgenographic technics to study stroke volume and heart size, concluded that all the nitrates and nitrites decreased stroke volume and heart size and caused a tachycardia so that the effect on cardiac output was insignificant in most cases. However, in those subjects whose rates were markedly accelerated, a rise in cardiac output of up to 30 per cent was noted. The authors also concluded from the ballistocardiographic findings that the velocity of ejection was markedly increased. They ascribed the reduced stroke volume and decreased heart size to deficient venous return of blood to the heart, since these effects were magnified by assuming an upright posture. Honig et al.,[11] in an excellent study using a flowmeter in dogs and a ballistocardiogram in humans, reported that nitroglycerine caused a 10 to 55 per cent increase in cardiac output at the point of greatest fall in diastolic pressure. Cardiac output remained elevated for three and a half minutes and then fell below the control level; stroke volume and velocity and acceleration of blood increased in all cases. Cardiac output was increased to a greater extent than venous

* From the Cardiac Clinic, Groote Schuur Hospital and C.S.I.R. Cardio-Pulmonary Research Group, Department of Medicine, University of Cape Town, South Africa. Part of the expenses for this work have been defrayed by grants received from the Council for Scientific and Industrial Research and the City Council of Cape Town.

TABLE I

Hemodynamic Effects of Administration of Amyl Nitrite and Phenylephrine

Case No.	Sex and Age (yr.)	Diagnosis	Drug	Pressures (mm. Hg)					Cardiac Output (L./min.)		Heart Rate (per min.)	Stroke Volume (c.c.)	Total Systemic Resistance (units)	Mean Recirculation Time (sec.)	M_1-A_2 Interval (sec.)
				Systemic S/D	Mean	RV	PA	Mean PA Wedge	Fick	Dye					
1	M, 31	Mild pulmonary stenosis	Control	132/80	97	42/6	22/10	...	8.1	5.6	72	78	17.4	18	0.29
			AN	80/50	60	72/10	...	...	...	16.0	114	140	3.8	14	0.24
			Control	130/82	96	37/5	...	...	...	6.5	70	93	15.0	18	0.29
			PE, 0.7 mg.	165/105	125	57/15	...	...	...	4.3	50	86	29.0	32	0.33
2	M, 24	Patent ductus ligated 10 years previously; slight dilatation of pulmonary artery only at time of study	Control	105/65	78	42/5	40/22	...	6.0	5.4	60	90	14.5	26	0.31
			AN	90/45	60	50/7	...	...	...	16.1	84	190	3.7	22	0.28
			Control	100/57	71	40/7	...	...	...	5.4	64	84	13.0	26	0.30
			PE, 0.7 mg.	148/100	116	48/10	...	...	...	2.3	33	72	50	40	0.35
3	F, 15	Complete repair of ASD	Control	112/62	82	17/0	18/7	...	5.2	3.7	79	47	22.0	17	0.29
			AN	60/20	33	...	18/6	...	...	5.7	120	47	5.8	14	0.27
			Control	107/65	79	...	12/5	...	...	3.5	85	41	22.0	18	0.30
			PE, 0.4 mg.	145/75	98	...	20/12	...	...	2.0	50	40	49.0	25	0.38
4	F, 20	Postop. VSD; complete repair; normal pressures	Control	150/75	100	35/0	30/12	...	7.6	4.8	86	55	21.0	15	0.28
			AN	110/32	58	...	20/10	...	...	9.6	120	80	6.0	14	0.21
			Control	155/90	112	...	25/12	...	...	5.5	84	65	20.0	14	0.27
			PE, 0.5 mg.	260/130	173	...	40/15	...	...	2.3	45	51	75.0	22	0.31
5	M, 36	Postop. infundibular stenosis; no residual gradient at time of study	Control	120/65	83	28/2	26/10	...	5.5	4.2	65	65	20.0	19	0.30
			AN	95/30	55	...	26/10	...	...	9.0	86	104	6.1	17	0.26
			Control	155/90	112	...	22/10	...	...	4.5	60	75	25.0	20	0.29
			PE, 0.6 mg.	180/110	133	...	50/20	...	...	3.1	42	74	43.0	30	0.39
6	M, 24	Mild pulmonary stenosis	Control	125/75	92	38/2	19/6	...	5.4	3.6	88	46	23.0	19	0.30
			AN	100/50	67	60/2	...	...	...	5.0	94	47	12.5	16	0.26
			Control	135/75	95	42/0	...	...	...	3.8	83	41	25.0	18	0.30
			PE, 0.5 mg.	190/100	130	50/10	...	...	...	2.8	60	53	46.0	19	0.35
7	F, 11	Mild pulmonary stenosis	Control	160/100	120	40/0	24/10	...	3.4	3.3	95	35	36.0	14	0.28
			AN	110/65	80	...	22/12	...	...	5.6	143	39	14.0	11	0.24
			Control	145/95	112	...	20/14	...	...	3.3	105	31	34.0	14	0.27
			PE, 0.7 mg.	170/125	143	...	30/17	...	...	2.2	65	34	65.0	20	0.36
8	M, 8	Postop. VSD; complete repair; slight residual elevation of PA pressures	Control	110/60	77	36/0	36/12	...	5.0	5.1	80	66	15.0	14	...
			AN	60/37	45	...	...	...	...	9.6	140	72	4.7	14	...
			Control	90/50	63	...	34/8	...	...	5.1	77	64	12.0	14	...
			PE, 0.6 mg.	137/80	99	...	56/20	...	...	4.3	60	68	23.0	17	...
9	F, 13	Postop. ASD; complete repair	Control	135/80	98	26/3	22/15	...	3.2	4.3	91	47	23.0	13	...
			AN	100/50	67	...	18/12	...	...	6.8	110	62	10.8	11	...
			Control	130/75	93	...	20/12	...	...	5.3	99	54	18.0	13	...
			PE, 0.6 mg.	200/115	143	...	38/24	...	...	2.3	55	45	32.0	32	...
10	F, 32	Postop. ASD; complete repair	Control	105/55	72	20/0	16/5	3	3.6	3.5	85	41	20.5	22	...
			AN	50/25	33	...	15/5	2	...	4.9	105	47	6.8	22	...
			Control	110/50	70	...	15/5	1	...	3.9	84	46	18.0	22	...
			PE, 0.6 mg.	190/75	113	...	30/15	10	...	3.1	48	65	33.0	26	...
11	M, 11	Postop. VSD; complete repair; slight residual elevation of PA pressure	Control	150/75	100	35/5	35/20	...	4.9	5.3	100	53	19.0	14	0.26
			AN	85/37	52	...	40/20	...	...	9.1	150	61	5.8	13	0.20
			Control	142/80	101	...	40/20	...	...	5.3	115	46	19.0	14	0.24
			PE, 0.5 mg.	160/95	117	...	50/20	...	...	4.1	70	59	28.0	19	0.31
12	F, 13	Aortic ejection sound; normal heart at catheterization	Control	85/55	65	20/0	20/12	...	5.3	3.7	120	31	17.0	16	...
			AN	52/35	41	...	...	...	...	6.0	150	40	6.8	13	...
			Control	87/62	70	...	...	...	...	5.4	102	53	13.0	16	...
			PE, 0.6 mg.	125/75	92	...	...	...	...	4.0	65	61	23.0	19	...
13	F, 25	Complete repair ASD	Control	130/75	93	12/0	12/5	2	3.5	4.2	95	44	23.0	15	...
			AN	100/42	62	...	15/7	2	...	5.4	125	43	11.0	13	...
			Control	137/82	100	...	12/4	2	...	4.5	92	49	22.0	15	...
			PE, 0.5 mg.	205/105	138	...	38/21	20	...	3.9	75	52	34.0	20	...

Abbreviations in this table are as follows: S/D = systolic and diastolic; RV = right ventricular pressure; PA = pulmonary artery pressure; mean PA wedge = mean pulmonary artery wedge pressure; M_1-A_2 interval = time interval between mitral component of first heart sound and aortic component of second heart sound; AN = amyl nitrite; PE = phenylephrine.

return, the difference being drawn from reserve blood volume in the thoracic reservoir. In general, the results indicate that when the blood pressure is lowered rapidly by nitrites the cardiac output is regularly increased.

Previous reports of the hemodynamic effects of phenylephrine[12,13] have demonstrated that this drug causes systemic vasoconstriction with an elevation of systemic pressure and reduction in cardiac output. In anesthetized dogs[14] phenylephrine produces pulmonary vasoconstriction, but the effect on pulmonary vessels has not been studied in man.

In this report hemodynamic studies with amyl nitrite and phenylephrine were undertaken in man, using the dye dilution technic to measure cardiac output, to explain the observed effects of the drugs on heart murmurs.

Methods

Thirteen patients were studied during routine cardiac catheterization (Table 1). Seven were patients studied one year following repair of atrial or ventricular septal defects. Five of these had completely normal dynamics and two patients who had had ventricular septal defect with high pulmonary arterial pressures preoperatively had slight residual elevation of pulmonary artery pressures at the time of study (Cases 4 and 12). All the defects in this group were shown by saturation and dye studies to be completely closed. Three patients had mild pulmonary stenosis with right ventricular pressures of about 40 mm. Hg. Two patients catheterized for murmurs of uncertain cause had normal hemodynamics. One patient (Case 5) catheterized one year after operation for severe infundibular stenosis had a right ventricular pressure within normal limits and no residual gradient in the right ventricular outflow tract.

Pressure measurements were made with a capacitance manometer via a cardiac catheter introduced into the right side of the heart while systemic pressure was recorded on an inductance manometer via a needle placed in a systemic artery (radial, brachial or femoral). Both systemic and right heart pressures were recorded on a six channel photographic recorder.

Dye dilution studies. A level of 5 cm. below the sternal angle was taken as the zero reference point.[15] Cardiac output was first determined by the Fick method. The oxygen uptake was measured by the collection of expired air for a three minute period and analyzing the gas content by the micro-Scholander technic. Blood samples for analysis of oxygen content by the method of Van Slyke and Neil were taken simultaneously from the pulmonary and systemic arteries during the collection of expired air. Thereafter, dye dilution curves were recorded at a systemic artery by drawing blood at a constant rate through a densitometer. Indocyanine green was used in doses of 2.5 to 5 mg. and the injections were made into the pulmonary artery. For the quantitative studies the densitometer was calibrated by drawing through it known concentrations of dye in the patient's blood and constructing a three-point calibration curve. Systemic and right heart pressures and a dye curve were recorded during the first control period. The patient then inhaled amyl nitrite from a crushed perle for ten to twenty seconds. As soon as the systemic blood pressure had fallen 20 mm. Hg the dilution curve was recorded and on its completion the systemic pressure had usually returned to nearly normal levels. The dye curve was thus recorded at the height of the effect of amyl nitrite.

After all pressures had returned to normal levels a dye dilution curve, right heart and systemic pressures were recorded during a second control period.

Thereafter, phenylephrine was administered via a cardiac catheter in a single dose of 0.4 to 0.7 mg. so as to produce a rise in systemic pressure of at least 20 mm. Hg. As soon as the pressure rise and bradycardia were established, pressures and a dilution curve were again recorded. In two patients, immediately consecutive pulmonary artery wedge pressure and pulmonary artery pressures were measured during the control period and following administration of phenylephrine.

In eight patients simultaneous phonocardiograms were recorded to determine the duration of systole during the control periods and during the effects of amyl nitrite and phenylephrine. All patients were studied in the supine position under sedation with mild barbiturate.

Calculations

The heart rate was calculated from the electrocardiogram and was taken as the average rate recorded during the inscription of the primary deflection of the dilution curves. The mean recirculation time was the time between the initial and the recirculation peaks of the dilution curves. *Cardiac output* was calculated from the Stewart Hamilton formula as follows:

$$\text{Cardiac Output} = \frac{\text{Dose of dye in mg.} \times 60}{\text{Mean concentration in mg./L} \times \text{the duration of the curve in seconds}}$$

Stroke volume was calculated by dividing the cardiac output by the heart rate and systemic resistance was expressed in simple units obtained by dividing mean systemic blood pressure by the cardiac output in liters per minute.

Results

Amyl Nitrite: The results are summarized in Table 1. After inhalation of amyl nitrite a marked drop in systemic blood pressure and

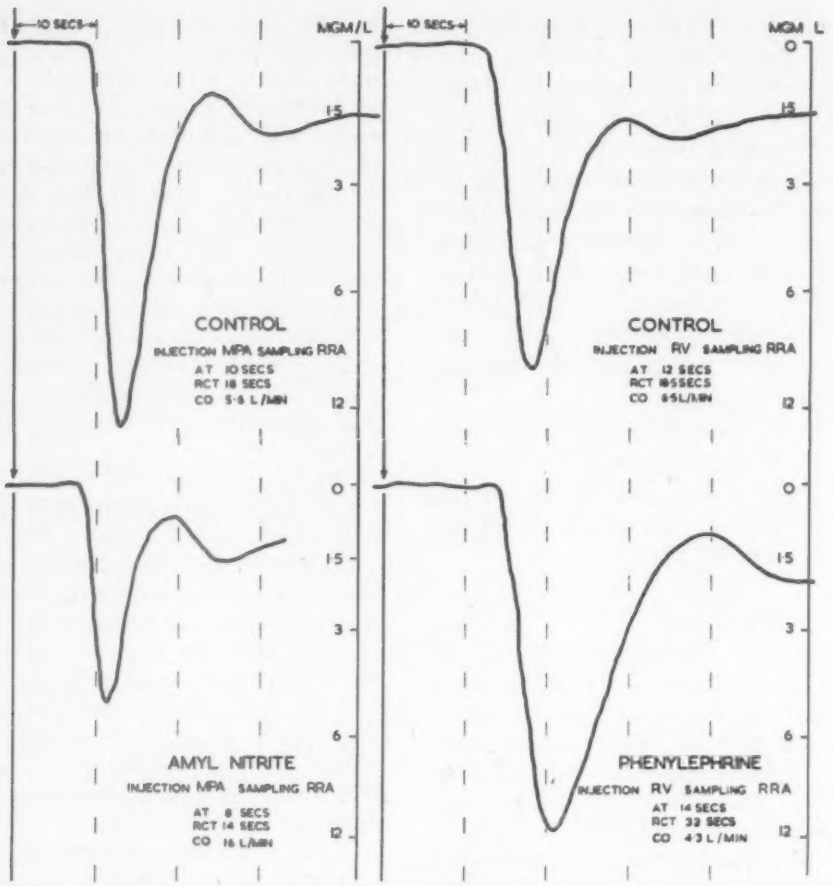


FIG. 1. Case 1. Dilution curves recorded at the radial artery following the injection of 5 mg. of indocyanine green into the pulmonary artery or right ventricle. *Upper left:* first control curve. *Lower left:* following inhalation of amyl nitrite. The time components of the curve are all diminished and the area enclosed by the primary deflection is much smaller, indicating shortening of the circulation time and substantial increase in cardiac output. *Upper right:* second control curve. *Lower right:* following administration of phenylephrine there is prolongation of all the time components and an increase in the area under the primary deflection, indicating marked slowing of the circulation and decrease in cardiac output.

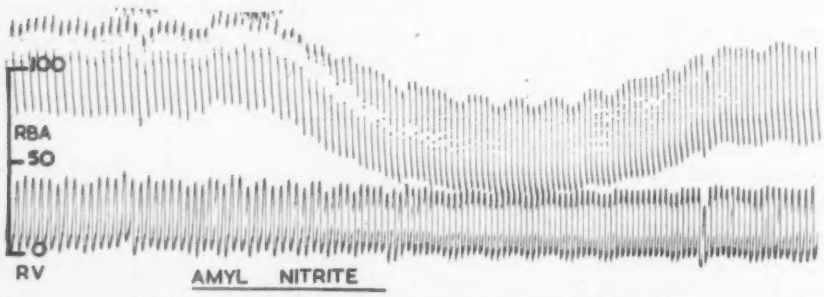


FIG. 2. *Amyl nitrite inhalation.* Simultaneous tracings of brachial artery (RBA) and right ventricular (RV) pressures in a case with normal hemodynamics. After amyl nitrite the systemic pressure falls abruptly then quickly returns towards the control level, whereas the right ventricular pressure is unchanged.

striking tachycardia occurred. Cardiac output was increased in all cases (Fig. 1) and the mean recirculation time was decreased in most. In contrast to the effects on the systemic circulation, right ventricular and pulmonary artery pressures were usually little affected (Fig. 2) although in two cases (Cases 1 and 6) with mild pulmonary stenosis, the right ven-

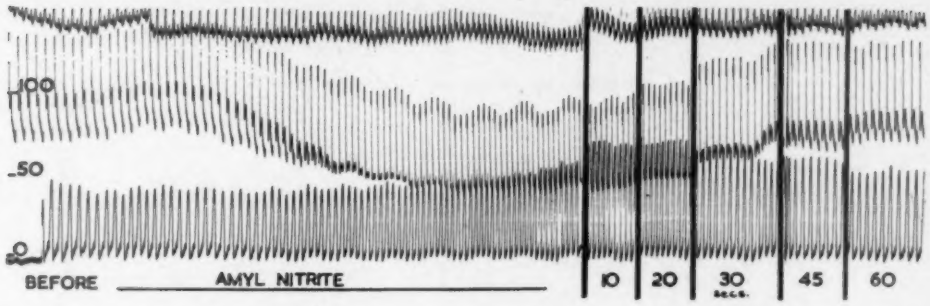


FIG. 3. *Amyl nitrite inhalation.* Simultaneous brachial artery (middle tracing) and right ventricular (lower tracing) pressures in a case with mild pulmonary stenosis, showing the drop in systemic pressure following inhalation of amyl nitrite and the slightly delayed rise in right ventricular pressure.

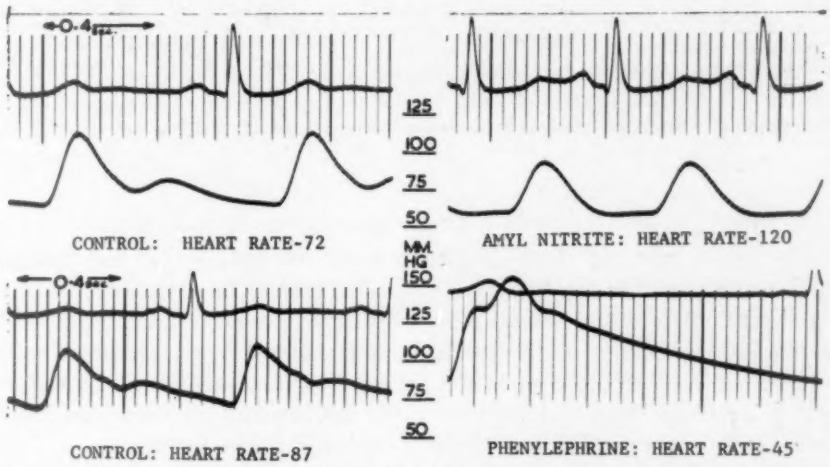


FIG. 4. *Comparison of effects of amyl nitrite and phenylephrine.* The arterial pressure pulses during the control studies are seen in the two panels on the left. *Upper right:* pressure pulse after amyl nitrite inhalation. Note the tachycardia, drop in systolic and diastolic pressures, smaller pulse pressure and disappearance of the dicrotic notch. *Lower right:* pressure pulse following phenylephrine administration. There is a profound bradycardia, rise in systemic and diastolic pressures, larger pulse pressure, a distinct anacrotic shoulder and a dicrotic notch occurring at a higher level on the descending limb of the pressure curve.

tricular pressure rose by 20 to 30 mm. Hg (Fig. 3). The arterial pressure curve showed characteristic changes (Fig. 4). Systolic pressures fell more than did the diastolic so that in most cases the pulse pressure decreased. In only one case did the pulse pressure increase slightly, from 55 to 65 mm. Hg. As the blood pressure fell the position of the dicrotic notch progressively moved to a lower level on the descending limb of the pressure curve, so that at the nadir of the hypotensive phase it had merged with the diastolic trough (Figs. 2 and 4). Calculated systemic resistance was obviously greatly reduced since mean pressure fell while the output increased.

Only slight changes in stroke volume were calculated in most cases; in seven there was virtually no change but in three patients with a slow heart rate at rest (Cases 1, 2 and 5) stroke volume increased considerably (by 62, 100 and 39 ml., respectively).

The duration of both systole and diastole were shortened; the systolic period by an average of 0.04 second and the diastolic by an average of 0.18 second. Amyl nitrite had its maximal effect on the blood pressure within thirty seconds of starting the inhalation and the blood pressure returned to the control level within one to one and a half minutes.

Phenylephrine: This agent produced changes directly opposed to those seen with amyl nitrite. A marked rise in systemic pressure and a profound bradycardia occurred; cardiac output was always decreased and the recirculation time strikingly prolonged (Fig. 1.) The decrease in cardiac output was usually proportional

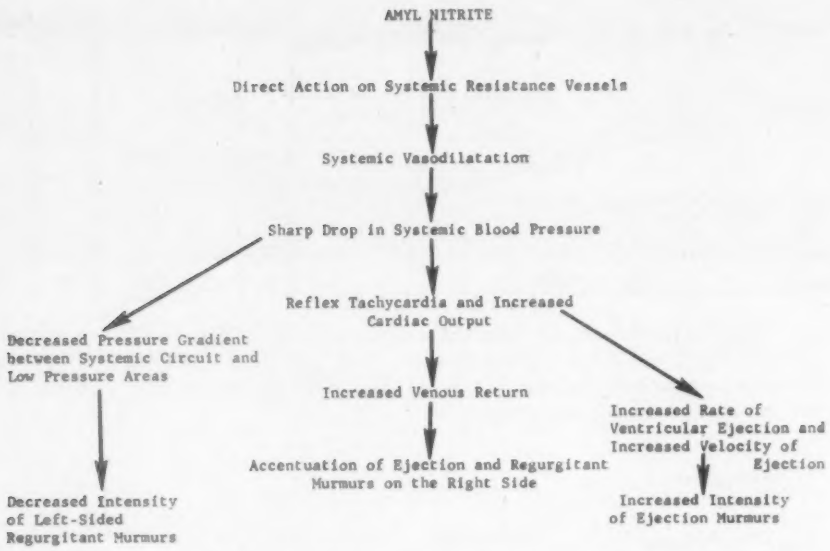


FIG. 5. Suggested mode of action of amyl nitrite on cardiac murmurs.

to the decrease in heart rate so that stroke volume showed slight and variable changes.

Pressures in the right ventricle and pulmonary artery were always increased but to a much smaller extent than the systemic pressure. In two patients (Cases 10 and 13) whose pulmonary artery and wedge pressures were measured at the height of the action of phenylephrine, the pulmonary artery pressure was disproportionately elevated so that the gradient across the pulmonary bed was slightly increased.

The arterial pressure curve showed characteristic changes (Fig. 4). The pulse pressure always increased. A well-marked anacrotic notch usually emerged, occurring high on the upstroke and the dicrotic notch progressively moved up the descending limb of the curve so that at the peak of the hypertensive action it approached the systolic peak of the pressure curve. The duration of systole was prolonged by an average of 0.06 second.

The effect of phenylephrine persisted for two to three minutes after which the blood pressure gradually returned to normal levels over a period of about eight minutes.

COMMENTS

Investigation of the hemodynamic effects of drugs with such acute and short-lived actions, such as amyl nitrite in the human subject, is difficult. Whereas pressure changes are easy to measure, determination of blood flow during an unsteady state presents a major problem. The usual method, using the Fick principle, requires a steady state maintained for the three to four minute period during which the samples of air and blood are collected. This method is clearly unsuitable for measuring the rapidly changing and transitory effects of amyl nitrite on blood flow.

An ideal method would detect beat to beat change in output (as with a flowmeter) but this is not readily applicable to human subjects during routine catheterization studies. Deductions from the pulse pressure and ballistocardiographic curves also have the disadvantages of all indirect methods.[16] In addition, it is conceivable that amyl nitrite and phenylephrine would affect the distensibility of the arterial system and so alter the pressure-volume relationships that calculations based on a fixed relationship would be unreliable.

From our point of view it seemed that the dilution method offered a partial solution to the problem, since the time taken from the injection to the completion of the primary deflection of a dilution curve at a systemic artery following injection of indicator into the pulmonary artery is usually not more than twenty seconds. Although a steady state is probably never attained following amyl nitrite inhalation, making accurate quantitation impossible, it seems likely that some idea of the changes in output can be determined. Certainly, the directional changes will be ascertained. Furthermore, the mean recirculation time can be

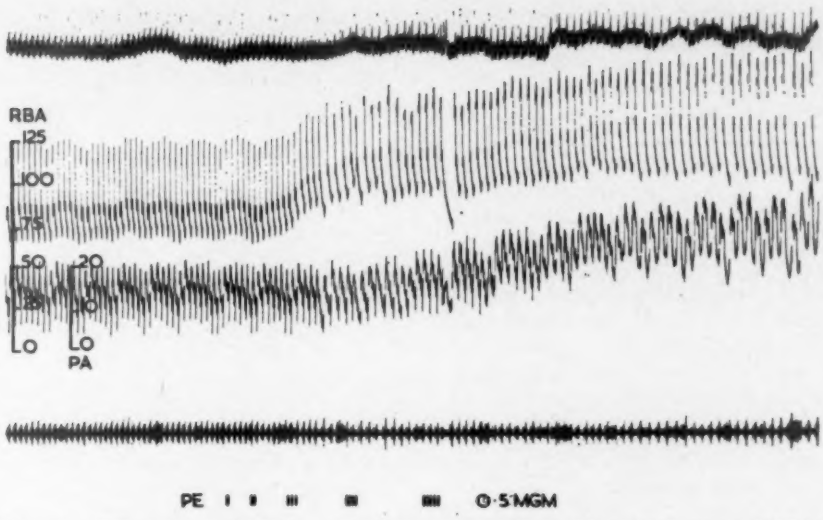


FIG. 6. *Effect of phenylephrine.* Simultaneous tracing of brachial artery (RBA) and pulmonary artery (PA) pressures following administration of 0.5 mg. of phenylephrine. Pulmonary artery pressure rises less than does the systemic pressure.

readily calculated, providing another parameter for assessing changes in flow.

These criticisms do not apply to the same extent to the studies of phenylephrine for in these the effects are sustained for a few minutes following a single injection, allowing reasonably accurate determinations of flow. Bearing in mind the limitations of the method of flow determinations in these circumstances, certain conclusions can nevertheless be drawn.

Amyl nitrite has clearly been shown to cause a pronounced drop in systemic pressure whereas the right ventricular and pulmonary artery pressures show only slight changes. In the presence of even mild pulmonary stenosis right ventricular pressures rise significantly as has been shown in this study and in others.[1]

Following inhalation of amyl nitrite the cardiac output is invariably increased by a significant amount; according to our calculations stroke volume is but little affected in most cases, the tachycardia resulting from inhibition of the carotid sinus and aortic baroceptors being nearly proportional to the increase in flow. In three cases with slow resting rates of 72, 60 and 65, significant increases in stroke volume were calculated (Cases 1, 2 and 5). In no case did stroke volume decrease significantly.

The shortening of the systolic ejection period associated with the tachycardia must, therefore, result in a greater velocity of systolic ejection even if the stroke volume remains unchanged. Although the present study has not conclusively demonstrated an increased venous return after amyl nitrite, it can be reasonably inferred that this does, in fact, occur. The striking increase in right ventricular pressure following inhalation of amyl nitrite in the presence of pulmonary stenosis can only be explained by an increase in venous return. Mean recirculation times were usually shorter following amyl nitrite and it is unlikely that this would occur if peripheral venous pooling and a reduction in venous return had been the dominant effect. Lastly, it seems unlikely that the increased forward flow could be due solely to shift of the central blood volume to the periphery. The reserve of blood in the lungs and heart is probably insufficient to support increases in output of this magnitude without an increase in the venous return.

The increased forward flow and greater velocity of ejection can be held responsible for the accentuation of ejection murmurs (Fallot's tetralogy excepted), and the increase in all right-sided murmurs can be attributed to the increased return of blood to the right heart. It would seem reasonable to attribute the softening in left-sided regurgitant murmurs to the fall in systemic and thus left ventricular pressure, reducing the pressure gradient responsible for the flow of blood through the incompetent valve or defect. These effects are summarized in Figure 5.

Our studies with phenylephrine confirm the findings of other authors using different methods of determination, of output[12,13] and are

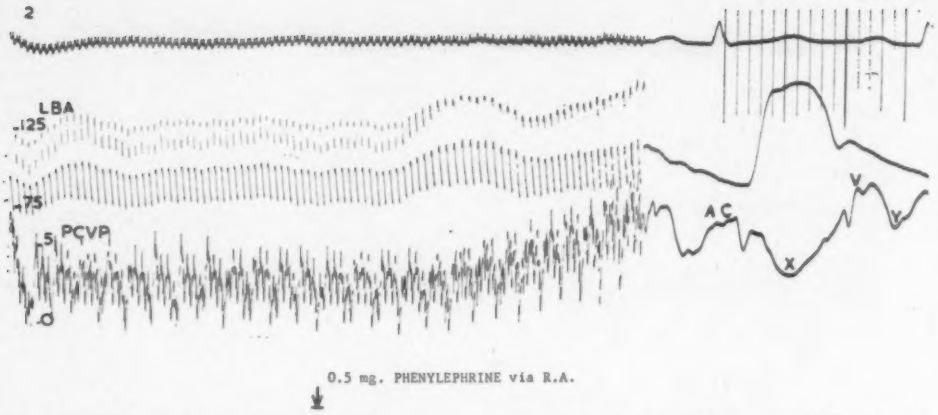


FIG. 7. *Effect of phenylephrine.* Simultaneous tracings of brachial artery (LBA) and pulmonary artery wedge (PCVP) pressures showing the simultaneous elevation of systemic and wedge pressures.

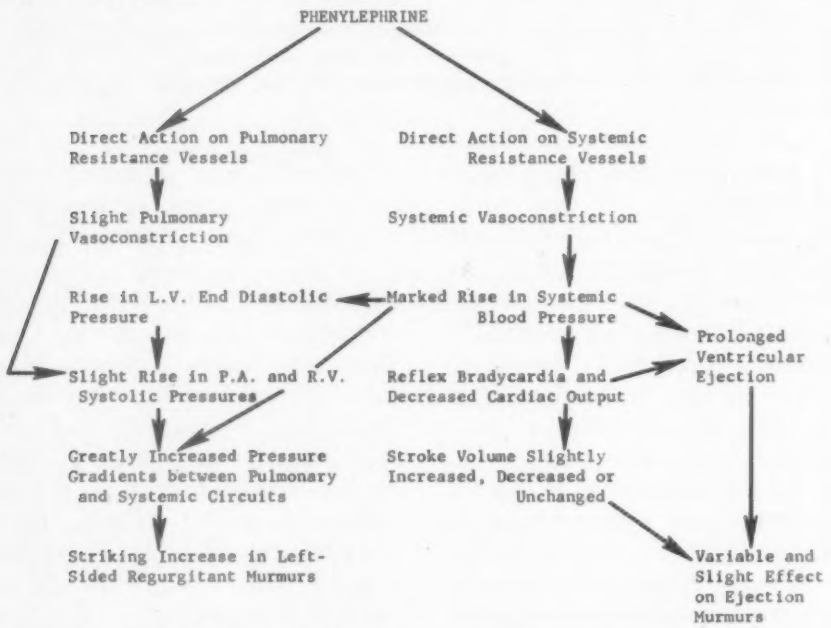


FIG. 8. Suggested mode of action of phenylephrine on cardiac murmurs.

similar to the studies reported with methoxamine,[17] a drug with the same general characteristics as phenylephrine. The most striking effect of phenylephrine is a rise in systemic pressure. The pressure in the pulmonary circuit rises less than the systemic pressure (Fig. 6) and is chiefly due to the rise in left ventricular end diastolic pressure (Fig. 7). However, in our two cases (Cases 10 and 13) in which wedge pressures and pulmonary artery pressures were measured consecutively there appeared to be a disproportionate rise in pulmonary artery pressure, so that the pressure gradient across the pulmonary vascular bed appeared to be slightly increased; this finding is supported by the animal experiments of Aviado and Schmidt[14] who noted that phenylephrine caused some degree of pulmonary vasoconstriction.

The over-all effect of these pressure changes, however, is a marked increase in pressure gradient between the systemic and pulmonary circuits and between the systemic circuits and other low pressure areas in the heart. This accounts for the increased intensity in left-sided regurgitant murmurs and the murmur of Fallot's tetralogy following administration of phenylephrine.[3] The cardiac output is always significantly decreased and the reflex bradycardia is usually more or less proportional to the decreased output so that stroke volume either remains unaltered or is slightly increased or decreased. The lengthening of the systolic ejection period associated with the bradycardia and the

variable changes in stroke volume probably account for the general tendency of ejection murmurs to be diminished in intensity after phenylephrine. The effects are summarized in Figure 8.

Summary

The effects of amyl nitrite and phenylephrine on the intracardiac pressures and cardiac output have been studied in a group of patients having either no hemodynamic abnormality or trivial pulmonary stenosis.

Amyl nitrite has been clearly demonstrated to decrease systemic pressures while pressures in the right side of the heart show no significant change, except in the presence of mild pulmonary stenosis. Cardiac output is increased and there is indirect evidence of an increased venous return to the heart.

Phenylephrine causes a marked rise in systemic pressure and a lesser rise in pressures of the right side of the heart, while cardiac output is always decreased.

The softening of left-sided regurgitant murmurs after amyl nitrite and their intensification following phenylephrine are explained on the basis of the changes in intracardiac pressures. Similarly, the intensification of ejection murmurs after amyl nitrite and the variable changes after administration of phenylephrine are discussed in relation to changes in cardiac output.

Acknowledgment

We wish to thank members of the staff of Groote Schuur Hospital for referring cases for investigation and the Superintendent, Dr. J. Burger, for his permission to publish them. We gratefully acknowledge the assistance of our technicians Mr. L. W. Piller, Mr. R. de Meneaud and Miss S. Joseph as well as the assistance of the nursing staff.

We are particularly grateful to the Council for Scientific and Industrial Research and City Council of Cape Town for their continued support.

References

1. Vogelpoel, L., Schrire, V., Nellen, M. and Swanepoel, A. The value of amyl nitrite in the differentiation of Fallot's tetralogy and pulmonary stenosis with intact ventricular septum. *Am. Heart J.*, 57: 803, 1959.
2. Vogelpoel, L., Nellen, M., Swanepoel, A. and Schrire, V. The use of amyl nitrite in the diagnosis of systolic murmurs. *Lancet*, 2: 810, 1959.
3. Vogelpoel, L., Schrire, V., Nellen, M. and Swanepoel, A. The use of phenylephrine in the differentiation of Fallot's tetralogy from pulmonary stenosis with intact ventricular septum. *Am. Heart J.*, 59: 489, 1960.
4. Barlow, J. and Shillingford, J. The use of amyl nitrite in differentiating mitral and aortic systolic murmurs. *Brit. Heart J.*, 20: 162, 1958.
5. Besterman, E. M. M. The use of phenylephrine to aid auscultation of early rheumatic diastolic murmurs. *Brit. Med. J.*, 2: 205, 1951.
6. Lindhard, J. and Jarisch, A. Uber das Minutemvolum des Herzens bei Ruhe und bei Muskelarbeit. *Arch. ges. Physiol.*, 161: 233, 1915.
7. Weiss, S. and Ellis, L. B. The influence of sodium nitrite on the cardiovascular system and on renal activity in health, in arterial hypertension and renal disease. *Arch. Int. Med.*, 52: 105, 1933.
8. Starr, I., Gamble, C. J., Margolies, A., Donal, J. S., Jr., Joseph, N. and Eagle, E. A clinical study of the action of 10 commonly used drugs on cardiac output, work and size, on respiration, on metabolic rate and on the electrocardiogram. *J. Clin. Invest.*, 16: 799, 1937.
9. Lauber, H. and Brauch, F. Uber pharmakologische Beeinflussung der Zirkulationsgrösse und Herzarbeit des Menschen. *Ztschr. klin. Med.*, 114: 120, 1930.
10. Brandt, J. L., Caccese, A. and Dock, W. Slit-kymographic evidence that nitroglycerine decreases heart volume and stroke volume while increasing the amplitude of ballistocardiographic waves. *Am. J. Med.*, 12: 650, 1952.
11. Honig, C. R., Tenney, S. M. and Gabel, P. V. The mechanism of cardiovascular action of nitroglycerine. An example of integrated response during the unsteady state. *Am. J. Med.*, 29: 910, 1960.
12. Keys, A. and Violante, A. Cardiocirculatory effects in man of neosynephrine (1-hydroxy B methyl amino-3 hydroxyethylbenzene hydrochloride). *J. Clin. Invest.*, 21: 1, 1942.
13. Horvath, S. M. and Knapp, D. W. Hemodynamic effects of neosynephrine. *Am. J. Physiol.*, 178: 386, 1954.
14. Aviado, D. M. and Schmidt, C. F. Effects of sympathomimetic drugs on pulmonary circulation. *J. Pharmacol. & Exper. Therap.*, 120: 512, 1957.
15. Bloomfield, R. A., Lausen, H. D., Cournand, A., Breed, E. S. and Richards, D. W. Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardiac circulatory diseases. *J. Clin. Invest.*, 25: 639, 1946.
16. Warner, H. R. Quantitation of stroke volume changes in man from the central pressure pulse. *Minnesota Med.*, 37: 111, 1954.
17. Stanfield, C. A. and Yu, P. N. The hemodynamic effects of methoxamine in mitral valve disease. *Circulation Res.*, 8: 895, 1960.

Heart Sounds in Atrial Tumors*

GEORG KAUFMANN, M.D., WILLI RUTISHAUSER, M.D. *and* ROBERT HEGGLIN, M.D.
Zurich, Switzerland

PRIMARY TUMORS of the atria are rare. The clinical signs of this condition are similar to those of mitral stenosis or tricuspid stenosis. Peculiar features are atypical murmurs, and their marked spontaneous variations during a short period of time and with postural changes.[1] The mitral opening snap is usually absent in left atrial tumors but there are exceptions to this rule.[2,3] At present, a correct clinical diagnosis is not made in the majority of cases.

Few phonocardiograms of patients with atrial tumors have been published. The behavior of the first and second heart sounds has not been subjected to close examination. The purpose of the present work is the analysis of the heart sounds in three cases of atrial tumors, with special reference to hemodynamics. We follow the common thought that the main components of the first and second sounds are the result of the closure of the atrioventricular and semilunar valves.[4,5] The first sound normally has the following sequence: mitral closure–tricuspid closure (M_1-T_1). The second sound has the sequence: aortic closure–pulmonary closure (A_2-P_2). Splitting of the first sound as a result of slight asynchronism of the two ventricles may be up to 0.03 second. Splitting of the second sound varies with breathing, rarely exceeding 0.04 second in held expiration.

Identification of the four valvular closures can be made reliably by recording the pressure curves in the atria, the aorta and the pulmonary artery.[6] Good results are also obtained with electrokymography.[7,8] A certain identification can be made by comparing the amplitudes of the components of the sounds in various areas. M_1 is more distinct at the apex; T_1 is more distinct at the right or left lower sternal border; P_2 is loudest in the second left intercostal space and is not usually recorded at the apex.[4]

MATERIAL AND METHODS

Over a period of little more than one year, we observed three cases of atrial tumors in the Medical Outpatient Clinic of the Zurich University Hospital.[9] The cases were respectively, a right-sided tumor, a left-sided tumor, and a bilateral tumor. The phonocardiograms were recorded with a six channel electrocardiograph and four high-pass filters with the following frequency ranges: high frequency (h) = about 440 c.p.s. (nominal frequency = 250 c.p.s.); middle range frequencies (m_2) = about 220 c.p.s. (140 c.p.s.) and (m_1) = about 130 c.p.s. (70 c.p.s.); low frequencies (t) = about 20 to 40 c.p.s. (35 c.p.s.).[10]

In the illustrations Mh means record with microphone and filter for high frequencies, Mm_2 and Mm_1, records in the middle-range frequencies and Mt in low frequencies. The phonocardiogram was usually recorded in held expiration, but tracings were also recorded during normal respiration (Cases 1 and 3). The tracing of the carotid pulse was used in order to determine the aortic closure. Jugular pulse tracings were recorded as well, although they are less accurate for timing the heart sounds. Pressure curves of the right atrium and of the pulmonary artery served to identify tricuspid and pulmonary closures in Case 3.

The duration of systole is defined as the interval between the first and second heart sounds; i.e., the distance between closure of the atrioventricular and semilunar valves.[5] Meiners'[11] diagram of the normal ejection time was used to determine the normal range of systolic length in relation to the heart rate and 0.02 to 0.04 second is added for the isometric contraction phase. In contrast to the usual procedure, the intervals between the sounds were measured from peak to peak because the timing of the largest vibration is less influenced by changes in frequency than the beginning of a sound component. With our measurements Q-M_1 is about 0.02 second longer than the values in the literature.

RESULTS

CASE 1. T. A., a forty-eight year old woman, entered the hospital on January 11, 1960. *Electrocardiogram* showed sinus tachycardia, right axis deviation, right atrial hypertrophy and right ven-

* From the Medical Outpatient Clinic of the University Hospital, Zurich, Switzerland.

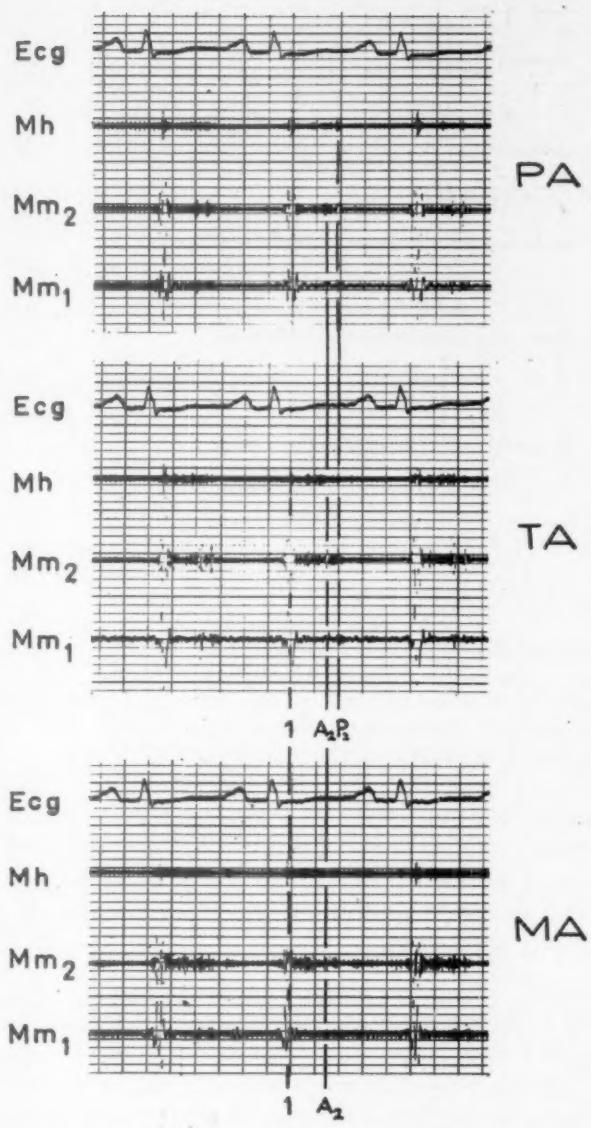


FIG. 1. Case 1. Left atrial tumor. Phonocardiogram in pulmonary area (PA), tricuspid area (TA) and mitral area (MA). Note delay of first sound (1), soft holosystolic murmur and premature aortic closure (A_2), causing distinct splitting of the second sound (A_2-P_2 = 0.04 second). Mh = high frequencies; Mm_2 and Mm_1 = medium frequencies.

tricular preponderance. There was slight right-sided delay of the intrinsicoid deflection as a result of right ventricular preponderance (0.04 second after Q in V_1). *Clinical diagnosis* was mitral stenosis. The course was rapidly downhill with collapse and death on January 15, 1960. *Autopsy* disclosed myxoma of the left atrium and evidence of pulmonary hypertension.

Phonocardiogram (November 18, 1959) recorded by Dr. K. Topaloğlu, Istanbul, seven weeks before entering clinic. First sound is narrowly split, M_1 presumably after T_1. Q-T_1 = 0.08 second; Q-M_1 = 0.11 second. Second sound is split; A_2-P_2 = 0.04–

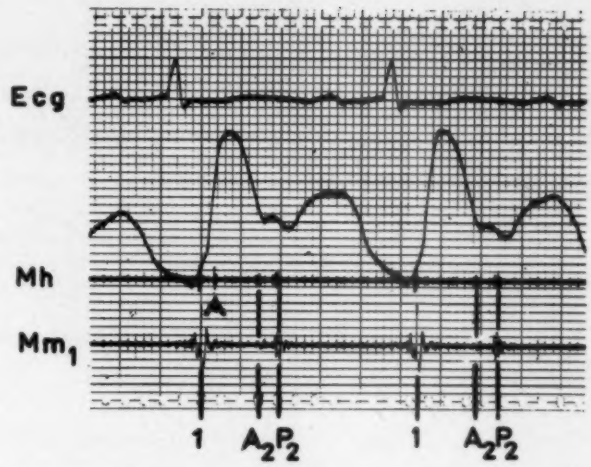


FIG. 2. Case 1. January 12, 1960. Carotid tracing and phonocardiogram recorded at lower left sternal margin. Note abnormally short left ventricular systole (1-A_2); aortic closure (A_2) is 0.01 second before dicrotic notch of carotid pulse tracing. A = artefact.

0.05 second. No murmur is recorded and there is no mitral opening snap. The length of systole of the right ventricle is 0.28 second, of the left ventricle, 0.20 second (standard range for heart rate of 102 is 0.24 to 0.32 second).

Phonocardiogram (January 12, 1960) (Fig. 1 and 2). First sound is broader, not clearly split, markedly delayed (maximum 0.10 second after Q). Holosystolic murmur of medium frequency recorded at lower left sternal border and apex. Early A_2 present, 0.16 second after the first sound. Second sound is split, A_2-P_2 = 0.04 second. There is no mitral opening snap. A short middiastolic murmur of medium frequency is present at the apex. Duration of systole of the right ventricle is 0.20 second; of the left ventricle, 0.16 second (standard range for heart rate of 112 is 0.24 to 0.31 second).

Phonocardiogram (January 14, 1960) (Fig. 3). First sound occurs 0.10 second after Q and is prolonged, with questionable paradoxical splitting. A_2 occurs early (0.14 second after first sound), with wide splitting of the second sound (A_2-P_2 = 0.06 second). Duration of systole of the right ventricle is 0.20 second; of the left ventricle, 0.14 second (standard range for heart rate of 104 is 0.25 to 0.32 second). No change in splitting of the second sound occurs during respiration.

Case Summary: Obstructive tumor of the left atrium. Phonocardiograms revealed abbreviation of left ventricular systole and holosystolic and middiastolic murmurs at the apex. There was no mitral opening snap or presystolic murmur (despite presence of sinus rhythm!). In the final stage, abbreviation of systole occurred on both sides, particularly on the left. With collapse on the day before death, extremely

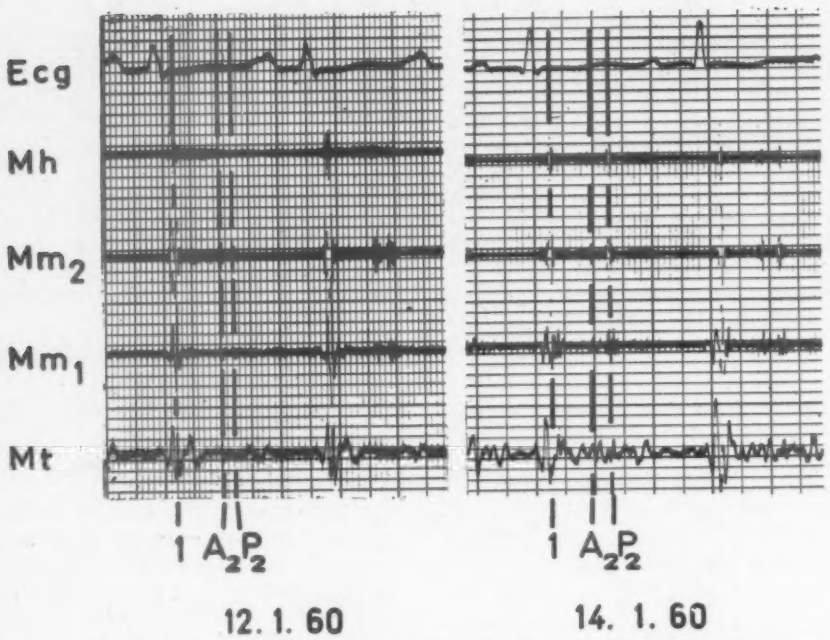


FIG. 3. Case 1. Phonocardiogram shows rapid change within two days. On January 14, 1960 there is earlier incidence of aortic closure (A_2), duration of left ventricular systole is shortened from 0.16 to 0.14 second, and splitting of the second sound is widened from 0.04 to 0.06 second. Electrical systole remains within standard range (Q-T = 0.30 second with heart rate of 104 per minute).

short systole and ejection time of the left ventricle were recorded.

CASE 2. L. M., a thirty-eight year old woman, was observed clinically from January 28 to March 12, 1959. There was evidence of marked venous congestion. *Electrocardiogram* showed sinus tachycardia and vertical electrical position. *Clinical diagnosis* was constrictive pericarditis. Sudden death caused by pulmonary embolism due to spontaneous detachment of a part of the tumor occurred at home on September 16, 1959. *Autopsy* disclosed myxoma of the right atrium.

Phonocardiogram (January 28, 1959) was similar to record of March 12, 1959. *Phonocardiogram* (March 12, 1959, Fig. 4). First sound is widely split. Q-M_1 = 0.08 second (normal), Q-T_1 = 0.18 second. There is no systolic murmur. Second sound is not split. A diastolic sound of low frequency occurs 0.11 second after the second sound, followed by a loud diastolic-presystolic murmur, extending as far as T_1. Duration of systole on the right is 0.18 second; on the left, 0.28 second (standard range for heart rate of 104 is 0.25 to 0.32 second).

Jugular pulse tracing showed very high *a* wave descending sharply to T_1, and small *c* and *v* waves without *x* descent.

Case Summary: Obstructive tumor of the right atrium. A loud diastolic-presystolic murmur was recorded at the right and left lower sternal borders. T_1 occurred very late, resulting in wide splitting of the first sound. Second sound was not split. A low frequency diastolic sound represented either the tricuspid opening sound or right ventricular third heart sound. The length of systole on the right was significantly shortened.

CASE 3. A. R., a thirty year old woman, was clinically observed from April 8, 1960 to June 10, 1960. She had had multiple emboli in the pulmonary circulation and probably also in the systemic circulation. *Electrocardiogram* showed sinus rhythm, vertical electrical position and right atrial hypertrophy. *Clinical diagnosis* was right atrial tumor and, in addition, possible left atrial tumor. Successful removal of a tangerine-size myxoma of the right atrium and of a walnut-size myxoma of the left atrium was carried out by Dr. Å. Senning, Clinic of Chest Surgery, Karolinska Hospital, Stockholm, with complete recovery.

Phonocardiogram (April 8, 1960). First sound was widely split; Q-M_1 = 0.09 second (slightly prolonged), Q-T_1 = 0.15 second. There was no systolic murmur. Second sound was split; A_2-P_2 = 0.04 second. There was a presystolic murmur at the right and left lower sternal borders extending to T_1, accentuated during inspiration. Duration of systole of the right ventricle was 0.24 second; of the left ventricle, 0.26 second (standard range for heart rate of 79 is 0.26 to 0.35 second). The *jugular pulse tracing* presented a very high *a* wave, descending sharply to T_1. There were small *c* and *v* waves without *x* descent.

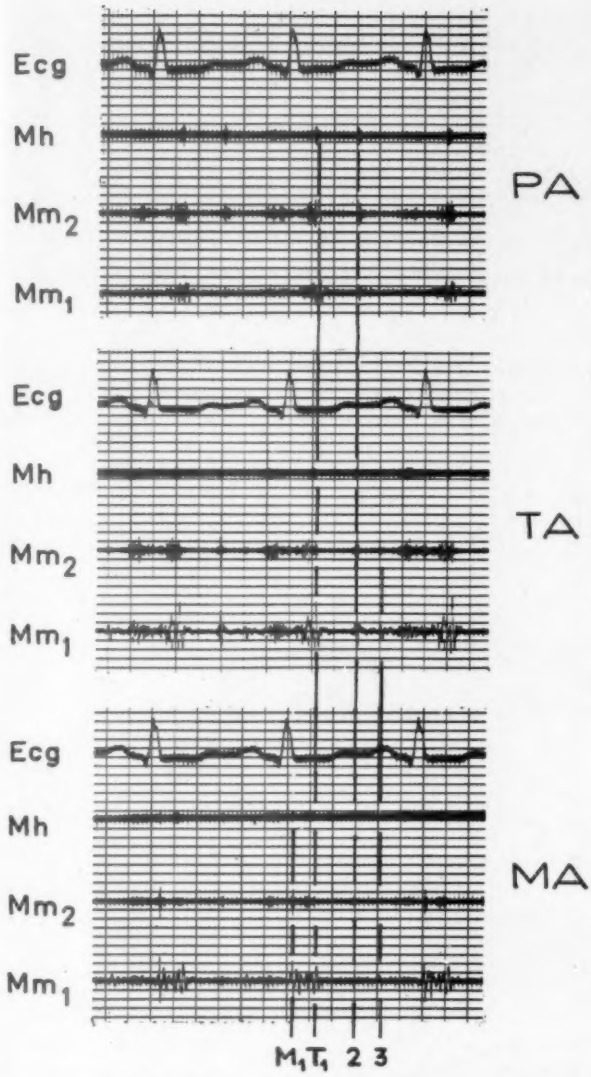


FIG. 4. Case 2. Right atrial tumor. Phonocardiogram shows a presystolic murmur at lower right sternal margin (TA), reaching as far as the delayed tricuspid component of the first sound ($Q\text{-}T_1$ = 0.18 second). The mitral component of first sound occurs at the normal time ($Q\text{-}M_1$ = 0.08 second). Note the wide splitting of the first sound, absence of a systolic murmur and the single second sound. The diastolic sound of low frequency 0.11 second after the second sound is either a tricuspid opening sound or an accentuated third heart sound.

Phonocardiogram (May 12, 1960, Fig. 5). Recorded during quiet respiration with simultaneous recording of the movements of the chest by photoelectric cell. There is marked variation in splitting of first and second sounds depending on the respiratory phase. At the end of inspiration, the first sound is narrowly split (0.03 second), while the second sound is widely split (0.06 second). At the end of expiration, the first sound is widely split (0.06 second), while the second sound is narrowly split (0.02 sec.). *Phonocardiogram* (May 24, 1960, Fig. 6). Recorded during quiet breathing with simultaneous recording of the pressure curve of the pulmonary artery and of the respiratory movement of the chest wall. There is marked variation in length of right ventricular systole, corresponding to variation in splitting of the sounds. There are minor changes in length of left ventricular systole. Systole of the right ventricle is abbreviated at the end of expiration. The duration of left ventricular systole varies within the standard range, contrary to the fluctuations in systolic duration of the right ventricle. The average pressure in the pulmonary artery was 25/8 mm. Hg with variations of pulse pressure parallel to those of right ventricular systolic duration.

Phonocardiogram (July 5, 1960). Three weeks after operation. $Q\text{-}M_1$ = 0.09 second (slightly prolonged); $Q\text{-}T_1$ = 0.13 second. Second sound is narrowly split (up to 0.02 second). There are no murmurs. *Phonocardiogram* (July 22, 1960, Fig. 6). Recorded during quiet breathing with simultaneous recording of the respiratory movement of the chest wall. Systole of the right and left ventricles are about equal in length and within standard range. There is no respiratory variation.

Case Summary: Myxoma of both atria, obstructive on the right. A presystolic murmur was present over the tricuspid area, accentuated in inspiration. Wide splitting of the first sound and splitting of the second sound occurred in held expiration. Unusually marked respiratory variations of sound splittings and of systolic duration of both ventricles were noted. At the end of expiration, the length of right ventricular systole was definitely shorter and the pressure amplitude in the pulmonary artery decreased. After surgical removal of the tumor, there was physiologic splitting of the first and second sounds without respiratory variations.

COMMENTS

All our observations were made in cases with sinus rhythm. The interpretation of cardiac sounds is still sometimes conjectural. The problem posed in Case 1 is whether there is really a wide splitting of the second sound or whether a mitral opening snap follows a single second sound. Evidence can be given against the latter assumption. The first component of the second sound is small in the pulmonary area and is not identifiable at all in the high frequency range (Fig. 2). In the presence of pulmonary hypertension, a single second sound would be accentuated in the second left interspace. Moreover, the interval between the two components of the second sound becomes greater with shortening of left ventricular systole (Fig. 3). On the contrary, a mitral opening shap would draw closer to the aortic

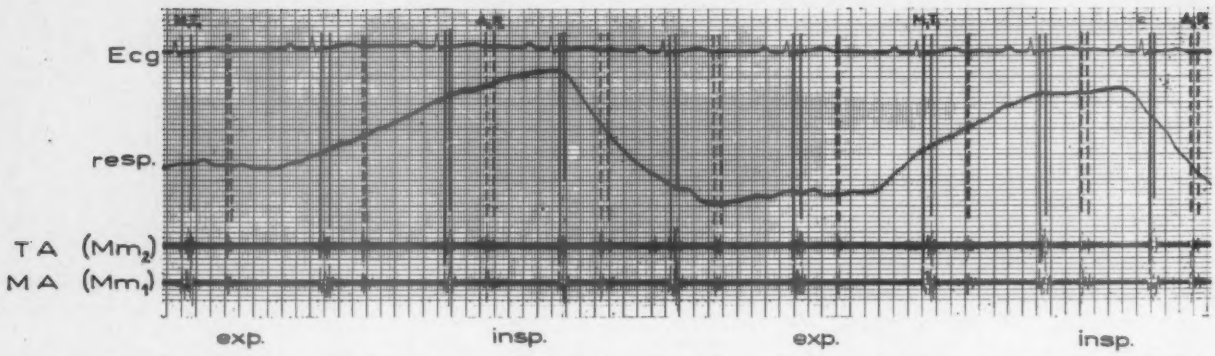


FIG. 5. Case 3. Bilateral atrial tumors, predominantly right-sided. Phonocardiogram recorded simultaneously at right lower sternal border (TA) and at apex (MA), together with recording of breathing movement of chest. First sound is narrowly split at end of inspiration, widely split at end of expiration. Second sound is widely split at end of inspiration, narrowly split at end of expiration.

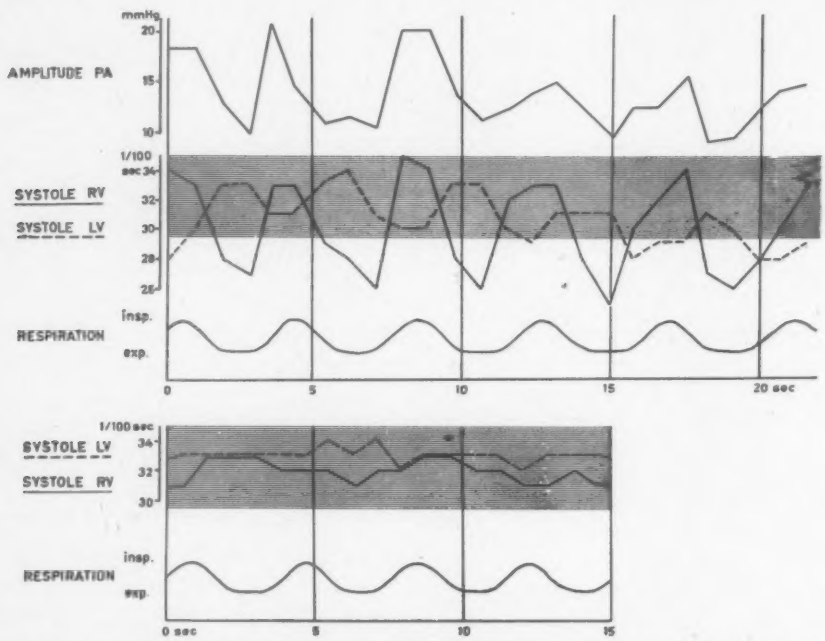


FIG. 6. Case 3. Respiratory variations in systolic duration of right and left ventricles. Shaded areas = normal range. *Above*, systole of the right ventricle is markedly shortened at end of expiration, paralleling the fall in systolic-diastolic pressure difference in pulmonary artery (amplitude PA). A minor variation occurs in systolic length of the left ventricle, opposite to that of the right ventricle. *Below*, same patient six weeks after surgical removal of the atrial tumors. Duration of systole of both ventricles is within standard range, and there is no respiratory variation.

component of the second sound with reduced ventricular filling, which occurs in mitral stenosis with atrial fibrillation.

In Case 2, the question arises whether the apparent splitting of the first sound is actually a first sound followed by an early systolic click. Identification of the second component with the closure of the tricuspid valve is supported by the presystolic murmur and by the *a* wave in the venous pulse tracing, both extending to the second component of the first sound. The phonocardiograms of the three cases of atrial tumors reveal several characteristic aspects.

Shortening of Mechanical Systole: On the side of the tumor, closure of the atrioventricular valve is often delayed, while closure of the semilunar valve tends to be premature. This causes abbreviation of mechanical systole of one ventricle. In general, severe stenosis of the atrioventricular valves produces the same phenomenon. Delay of the mitral component and even reversed splitting of the first sound are known to occur in mitral stenosis.[4,12] The interval Q – M_1 is related to the increase of pressure in the left atrium.[13,14] Slight shortening of ejection time with premature aortic component

TABLE 1
Duration of Ventricular Systole in Left and Right Atrial Tumors

Tumor	Duration of Ventricular Systole (sec.)*		
	Right	Left	Standard Range
Left atrial tumors			
Case 1			
Nov. 11, 1959	0.28	*0.20*	0.24–0.32
Jan. 12, 1960	*0.20*	*0.16*	0.24–0.31
Jan. 14, 1960	*0.20*	*0.14*	0.25–0.32
Lefcoe et al.[3]	?	*0.18–0.22*	0.25–0.32
McKusick[5]			0.26–0.34
Fig. 300	?	±0.26	
Right atrial tumors			
Case 2			
Mar. 12, 1959	*0.18*	0.28	0.25–0.32
Case 3			
April 8, 1960	*0.24*	0.26	0.26–0.35
May 24, 1960	*0.25*–0.35	*0.28*–0.34	0.29–0.37
Wyss et al.[17]			
Nov. 18, 1953	*0.26*?	0.34	0.29–0.37
May 18, 1954	*0.23*	0.29	0.27–0.35
Ashman et al.[18]			
Recumbent	0.28?	?	0.26–0.33
Sitting	*0.22*	?	0.24–0.31

* Abnormal values in italics.

of the second sound also occurs in mitral stenosis[15] but is more characteristic in mitral incompetence.

In rheumatic tricuspid stenosis, the first sound is difficult to analyze because the mitral and aortic valves are often damaged as well. Nevertheless, a wide splitting of the first sound; i.e., a delay of the tricuspid component, seems to be present in the case of Hollman.[16]

Unilateral shortening of systole in atrial tumors is not a constant feature (Table 1) and differs only in degree from the findings of organic valvular stenosis. The extremely late occurrence of T_1, as observed in Case 2, was also observed in a case of angioreticuloma of the right side of the heart which, starting from the ventricular septum, had grown through the tricuspid orifice into the right atrium.[17] In that case, the main component of the first heart sound seems markedly delayed (0.14 to 0.17 second after Q) and is distinguished from the following systolic sounds.

A considerable delay of the main component of the first sound was noted in a case of a tumor of the left atrium reported by Lefcoe et al.[3] No unilateral abbreviation of systole may be deduced from the sound tracings of atrial tumors published by McKusick[5] and by Ashman et al.[18]

Splitting of Heart Sounds: The displacements

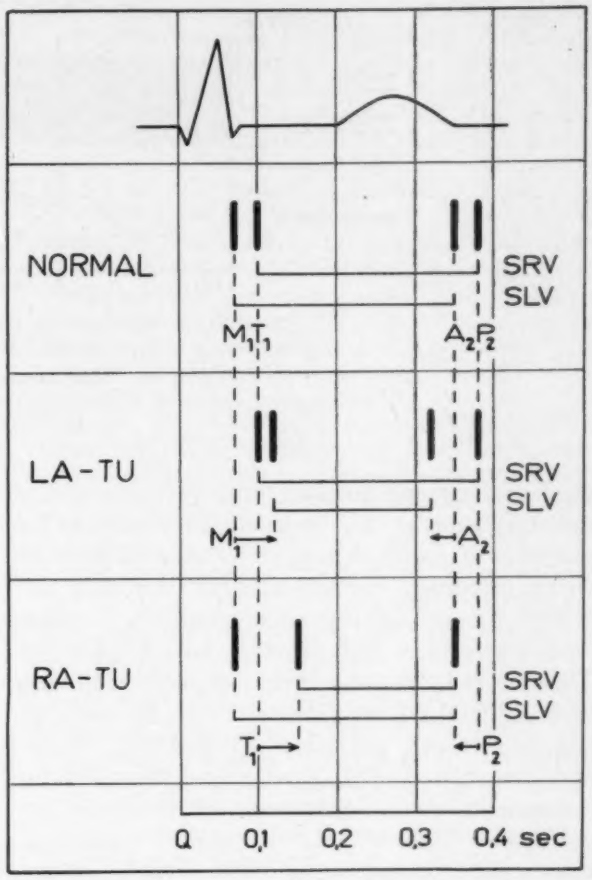


FIG. 7. Diagrammatic representation of the first and second heart sounds in obstructive atrial tumors. *Normal:* narrow splitting of first and second sounds, systole of right ventricle (SRV) and left ventricle (SLV) about equal in length. *Left atrial tumor* (LA-TU): fusion or reversed splitting of first sound, wide splitting of second sound, shortening of left ventricular systole. *Right atrial tumor* (RA-RU): wide splitting of first sound, narrow splitting or fusion of second sound, shortening of right ventricular systole.

of sound components in atrial tumors correspond to the following patterns (Fig. 7): In tumors of the left atrium, either the components of the first sound are fused or there is a reversed splitting; the second sound shows a wide splitting. In tumors of the right atrium, the first sound shows a wide splitting while the components of the second sound tend to fuse. These temporal displacements seem to be the result of markedly increased atrial pressure and of unilateral hypodynamic ventricular action. In atrial tumors, the cause of systolic shortening is mechanical in contrast to the primary metabolic ventricular hypodynamism, which has been described in certain forms of heart failure.[19]

Respiratory Variations of Systolic Length: In Case 3, with predominantly right atrial tumor,

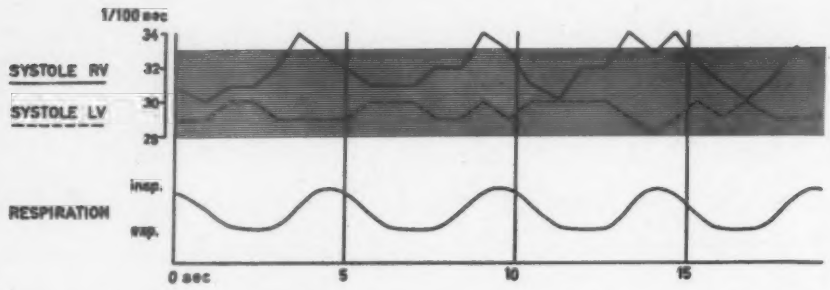


FIG. 8. Respiratory variations in systolic length of right and left ventricles in a healthy young man. Shaded area = normal range. Right ventricular systole is longest during inspiration, shortest during expiration. Suggestion of an opposite variation is noted in systolic length of the left ventricle.

we found exaggerated respiratory variations of systolic length. In normal conditions the duration of systole during quiet breathing varies within moderate limits. Systolic duration and stroke volume of the right ventricle increase with inspiration and decrease with expiration. The left ventricle shows the opposite variations in a reduced degree (Fig. 8).[20–22] In contrast, the respiratory variation in splitting of the first and second heart sounds, and therefore the changes in systolic duration, are greatly exaggerated in Case 3. At the end of expiration the marked shortening of right ventricular systole parallels the drop of pulse pressure in the pulmonary artery and, presumably, of the right ventricular stroke volume (Fig. 6). The tumor seems to obstruct the tricuspid orifice only at the end of expiration. This behavior depends on the size and location of the tumor and therefore is not constant. A similar mechanism is suggested in the phonocardiogram of a tumor of the left atrium reported by Lefcoe et al.[3] During six cycles of equal length, there is a marked variation of left ventricular systolic duration and a corresponding change of the interval between the second sound and the mitral opening snap. The shorter the systole, the shorter the interval from second sound to mitral snap. The pronounced variations are probably related to respiration.

Postural Changes: The duration of systole in atrial tumors can be altered by postural changes, as is shown in the tracings of Ashman et al.[18] in which the shortening of systole appeared only in the sitting position. The positional difference exceeded by far the normal postural variations.[23]

Increasing unilateral shortening of systole within a brief period of time may be significant for increasing obstruction of the atrioventricular orifice by an atrial tumor (Case 1).

SUMMARY

The phonocardiograms in three cases of atrial tumors are analyzed. The cases included one left-sided, one right-sided and one bilateral atrial tumor. There was marked homolateral shortening of systolic duration in two cases. Shortening of systole is compared with findings in stenosis of the mitral and tricuspid valves.

One case with predominantly right-sided atrial tumor showed abnormally large respiratory variations in the splitting of the heart sounds and in the length of right and left ventricular systole. The pulse pressure of the pulmonary artery paralleled the systolic duration of the right ventricle. The exaggerated respiratory variations disappeared after surgical removal of the tumor.

The following phonocardiographic signs should suggest the presence of an obstructive atrial tumor or thrombus: marked unilateral shortening of mechanical systole; exaggerated variation of systolic length with breathing, with postural changes, or within a short period of time. The phonocardiogram is an important diagnostic aid, particularly in the diagnosis of right atrial tumors, as there are few signs and clinical diagnosis seemed impossible as recently as fifteen years ago.

ACKNOWLEDGMENT

We are indebted to Mrs. E. Ungricht for technical assistance.

REFERENCES

1. MAHAIM, I. Les Tumeurs et les Polypes du Coeur. Etude Anatomo-clinique, pp. 91, 151. Paris-Lausanne, 1945. Masson et Roth.
2. SCHOLER, H. Klinische Besonderheiten der akut entstehenden Mitralfehler als Folgezustände von Vorhofgeschwülsten. *Cardiologia*, 31: 331, 1957.
3. LEFCOE, N. M., BRIEN, F. S. and MANNING, G. W.

An opening snap recorded in a case of tumor of the left atrium. *New England J. Med.*, 257: 178. 1957.

4. Leatham, A. Splitting of the first and second heart sounds. *Lancet*, 2: 607, 1954.
5. McKusick, V. A. Cardiovascular Sound in Health and Disease, pp. 123, 117, 307. Baltimore, 1958. Williams and Wilkins.
6. Braunwald, E., Fishman, A. P. and Cournand, A. Time relationship of dynamic events in the cardiac chambers, pulmonary artery and aorta in man. *Circulation Res.*, 4: 100, 1956.
7. Luisada, A. A. and Fleischner, F. G. Temporal relation between contraction of right and left sides of the normal human heart. *Proc. Soc. Exper. Biol. & Med.*, 66: 436, 1947.
8. Reinhold, J. and Rudhe, U. Relation of the first and second heart sounds to events in the cardiac cycle. *Brit. Heart J.*, 19: 473, 1957.
9. Lüthy, E. To be published.
10. Maass, H. and Weber, A. Herzschallregistrierung mittels differenzierender Filter. Eine Studie zur Herzschallnormung. *Cardiologia*, 21: 773, 1952.
11. Meiners, S. Messmethoden zur Analyse der Herz- und Kreislaufdynamik. Vorträge des ersten Freiburger Colloquiums über Kreislaufmessungen. München-Gräfelfing, 1958. Banaschewski.
12. McKusick, V. A., Reagan, W. P., Santos, G. W. and Webb, G. N. The splitting of heart sounds. *Am. J. Med.*, 19: 849, 1955.
13. Wells, B. G. Prediction of mitral pressure gradient from heart sounds. *Brit. Med. J.*, 1: 551, 1957.
14. Braunwald, E., Moscovitz, H. L., Amram, S. S., Lasser, R. P., Sapin, S. O., Himmelstein, A., Ravitch, M. M. and Gordon, A. J. The hemodynamics of the left side of the heart as studied by simultaneous left atrial, left ventricular, and aortic pressures; particular reference to mitral stenosis. *Circulation*, 12: 69, 1955.
15. Blumberger, K. Die Herzdynamik bei erworbenen Klappenfehlern. *Verh. dtsch. Ges. Kreislaufforsch.*, 20: 25, 1954.
16. Hollman, A. Tricuspid valvotomy. *Lancet*, 1: 535, 1956.
17. Wyss, S., Schlegel, J. J., Holzmann, M. and Hunziker, A. Angioretikulom des rechten Herzens mit dem Bild einer funktionellen Trikuspidalstenose. *Cardiologia*, 28: 174, 1956.
18. Ashman, H., Zaroff, L. I. and Baronofsky, I. Right atrial myxoma. *Am. J. Med.*, 28: 487, 1960.
19. Hegglin, R. Kritische Bemerkungen zum Problem des Myokardstoffwechsels vom Standpunkt des Klinikers. Bad Oeynhausener Gespräche III über Herzinsuffizienz und Digitaliseinwirkungen. Berlin-Göttingen-Heidelberg, 1959. Springer Verlag.
20. Shuler, R. H., Ensor, C., Gunning, R. E., Moss, W. G. and Johnson, V. The differential effects of respiration on the left and right ventricles. *Am. J. Physiol.*, 137: 620, 1942.
21. Lauson, H. D., Bloomfield, R. A. and Cournand, A. The influence of the respiration on the circulation in man. *Am. J. Med.*, 1: 315, 1946.
22. Williams, A. H. and Gropper, A. L. Interrelationships of cardiac output, blood pressure, and peripheral resistance during normal respiration in normotensive and hypertensive individuals. *Circulation*, 4: 278, 1951.
23. Lombard, W. P. and Cope, O. M. The duration of the systole of the left ventricle of man. *Am. J. Physiol.*, 77: 263, 1926.

Total Correction of Tetralogy of Fallot

Complications and Results*

J. David Bristow, M.D., Victor D. Menashe, M.D., Herbert E. Griswold, M.D. *and* Albert Starr, M.D.

Portland, Oregon

This paper presents a critical analysis of the early and late postoperative course following total correction of tetralogy of Fallot. Study of the clinical alterations produced by surgical correction is important in evaluating presently employed operative procedures. Such observations lead to a better understanding of the congenital malformations themselves and, with hemodynamic investigations, will ultimately indicate the effectiveness of current approaches to correction.

Twenty-eight patients comprise the experience with complete correction of tetralogy at the University of Oregon Medical School Hospital. The same operative technics were used consistently throughout the series and were performed during the period from March 25, 1959 to June 16, 1960.

The term "tetralogy of Fallot" has a variety of definitions; the following anatomic and physiologic criteria were outlined for acceptance of this diagnosis. Infundibular or valvular pulmonic stenosis is present and frequently both types are found. The ventricular septal defect characteristically is large and situated inferior to the crista supraventricularis, often involving both the anterior and membranous parts of the septum. The pulmonary artery may be hypoplastic or of normal size. Right and left ventricular and proximal aortic systolic pressures are equal; the ventricular defect is large enough to permit unrestricted flow from the right ventricle to the aorta. Thus, cyanosis is usually present.

Case Material

Pertinent findings in the twenty-eight patients are listed in Table 1. Seven had had previous systemic-pulmonary arterial anastomoses of Blalock-Taussig or Potts types. Only two of these were functioning at the time of total correction. Closed pulmonic valvotomy or infundibular resection had been performed previously in four cases without relief of the stenosis.

The series is a typical representation of the spectrum of severity which is seen with this disease. All but two cases had been observed to be continually or intermittently cyanotic. Abnormally high hemoglobin or hematocrit values were found in seventeen patients and eight had hematocrits above 60 per cent. Direct measurement of arterial oxygen saturation had been performed in seventeen patients and values below 94 per cent were found in fourteen of these. Congestive heart failure was absent in all patients before surgery.

The usual radiographic findings in tetralogy, consisting of normal or small over-all heart size, uplifting of the cardiac apex, concavity in the region of the main pulmonary artery and diminution of vascular markings in the lungs, were present in most cases. Some features were absent in several patients, however. Thus, prominence of poststenotic dilatation of the pulmonary artery was seen in five patients.

Of twenty patients whose angiocardiograms provided satisfactory right ventricular opacification, slight or moderate enlargement of this chamber was present in fifteen. All degrees of infundibular narrowing and pulmonary arterial size were noted. Almost all cases had evidence of right to left shunting through the ventricular septal defect as demonstrated by premature opacification of the aorta.

The electrocardiogram consistently was compatible with the diagnosis of tetralogy of Fallot. An R, rR′ or rsR′ complex was present in leads V_3R and V_1 in all. In the left precordial leads most tracings had an RS pattern, but in five there was a significant Q wave or an R/S ratio greater than 2.5, or both, suggesting left ventricular hypertrophy in addition. These five patients had little or no cyanosis and two had findings by cardiac catheterization of a minimal

* From the Division of Cardiology, Department of Medicine, the Division of Thoracic Surgery, Department of Surgery, and the Crippled Children's Division, University of Oregon Medical School, Portland, Oregon. This work was supported in part by a grant from the United States Public Health Service (USPHS #H 2151 (C4)).

TABLE I
Summary of Twenty-eight Cases

Preoperative Findings						Operation					Complications
Date of Surgery	Case No.	Age (yr.)	Weight (lb.)	Hematocrit (%) or Hemoglobin	Arterial Oxygen Saturation (%)	Size of Pulmonary Artery	Type of Pulmonary Stenosis	Perfusion Time (min.)	Arrest Time (min.) and Type	Temperature during Perfusion (°)	
3/25/59	1	16	99	57	76	Normal	I	49	9.5 K	Normal	No cardiac complications
4/8/59	2	10	55	56	86	Normal	I	50	14.5 K	Normal	
4/16/59	3	7	54	46	94	Small	I and V	53	14 K	Normal	
7/29/59	4	18	153	70	...	Normal	I and V	75	15 K	31.5	
10/15/59	5	8	47	42	98	Normal	I	55	12 K	34.5	
10/22/59	6	12	83	55	86	Small	I and V	120	14 K	29.0	
11/4/59	7	9	63	42	92	Normal	I	48	11.5 K	29.0	
11/5/59	8	7	47	38	98 (ear)	Normal	I	71	15.5 K	31.0	
12/10/59	9	6	41	49	66	Small	I and V	71	12 A	35.0	
12/31/59	10	7	51	42	89	Small	I and V	90	11.5 A	29.0	
1/6/60	11	7	53	17.6 gm. %	84	Small	I and V	57	11.5 A	33.0	
2/24/60	12	18	113	71	89	Normal	I	100	16 A	27.5	
5/26/60	13	11	98	53	...	Normal	I	57	16.5 A	32.5	
5/21/59	14	5	45	45	92	Very small	I	360	14 K	Normal	Low cardiac output syndrome
5/27/59	15	7	45	Report lost	...	Normal	I and V	62	26 K	Normal	
9/17/59	16	8	46	Report lost	...	Normal	I and V	150	16 K	30.0	
12/17/59	17	6	50	61	80 (ear)	Small	I	175	None	24.5	
1/7/60	18	16	122	53	89	Small	I and V	78	14 A	32.5	
9/9/59	19	18	88	46	89 (ear)	Atresia LPA	I	54	10 K	34.5	Low cardiac output syndrome; congestive heart failure
11/19/59	20	6	42	73	...	Atresia	Atresia	106	12 A	26.0	
6/11/59	21	3	34	41	76	Small	I and V	80	16 K	35.5	Congestive heart failure
7/2/59	22	4	28	52	85	Small	I and V	63	15 K	34.0	
12/2/59	23	5	35	65	66	Small	I and V	89	None	30.0	
1/28/60	24	4	32	65	...	Very small	I	66	15 A	32.0	
2/11/60	25	15	122	58	94	Normal	I	110	14 A	30.0	
2/17/60	26	8	50	66	79	Normal	I and V	68	13 A	31.0	
4/14/60	27	8	61	72	...	Small	I and V	83	20 A	29.0	
6/16/60	28	3	32	19.1 gm. %	...	Small	I and V	60	14.5 A	29.0	

Key to abbreviations: I = infundibular; V = valvular; K = potassium citrate; A = anoxic; ear = ear oximeter; LPA = left pulmonary artery.

left to right shunt. Right axis deviation in the frontal plane was found in all of the electrocardiograms, ranging from +99 to −150°. Six patients had evidence of right atrial hypertrophy, with P waves in lead II measuring 2.5 mm. or more in height. This finding was associated with marked cyanosis. There was no correlation between the degree of right ventricular hypertrophy found electrocardiographically and the severity of pulmonic obstruction observed at surgery.

Right heart catheterization had been performed in twenty-two of the twenty-eight cases. Right ventricular and systemic arterial systolic pressures were equal or close thereto in those in whom both were measured. Evidence of a left to right shunt was found in four patients, two of whom had systemic arterial undersaturation as well.

Surviving patients have been followed for an average period of 8.2 months, and six have been observed for one year or more since surgery.

OPERATION

Details of the surgical technic will be described in a separate report.[1] Correction was accomplished with the aid of cardiopulmonary bypass utilizing a pump oxygenator. A normal resting cardiac index was used as the perfusion rate, as outlined previously.[2] The total period of perfusion was between fifty and one hundred minutes in most cases. The ventricular septal defect was closed through a right ventriculotomy, using an Ivalon patch, and cardiac arrest was induced for placement of sutures around the margin of the defect. Potassium citrate was used as the arresting agent for the first half of the series. It was then replaced by anoxic arrest. The mean duration of elective arrest for the twenty-six patients

TABLE II
Complications and Results*

Case No.	Complications	Ultimate Result
1	None	Excellent
2	None	Excellent
3	None	Excellent
4	Reopening of VSD	Good; has asymptomatic left to right shunt
5	Cerebral embolus, without residual effect	Excellent
6	Reopening of VSD	Good; has asymptomatic left to right shunt
7	None	Excellent
8	None	Excellent
9	None	Excellent
10	None	Excellent
11	None	Excellent
12	None	Excellent
13	None	Excellent
14	Extensive infundibular resection; low CO synd	Died in surgery
15	Long potassium arrest; low CO synd	Died on 2nd po day
16	Unsatisfactory perfusion; low CO synd	Died in surgery
17	Extensive infundibular resection; low CO synd	Died on day of surgery
18	Low CO synd	Excellent
19	Low CO synd; chronic CHF	Good; no present signs of CHF
20	Low CO synd; chronic CHF	Good; no present signs of CHF
21	Chronic CHF; no VSD by cath findings (aneurysm OT)	Fair; no present signs of CHF
22	Transient mild CHF	Excellent
23	Heart block; transient CHF; appendicitis	Excellent
24	Chronic CHF	Good; no present signs of CHF
25	Reopened VSD with large shunt and severe CHF	Died; during reclosure of VSD, 2 months po
26	Heart block; chronic CHF	Good; no present signs of CHF
27	Transient mild CHF	Excellent
28	Transient mild CHF	Excellent

* Patients with excellent results are asymptomatic with unrestricted physical activity and are not receiving treatment for heart failure. Those classified as good have medically imposed moderate restriction of activity and continue to be treated for heart failure with digitalis and sodium restriction. Two additional patients are classified as good who have open VSD without symptoms.

Abbreviations: VSD = ventricular septal defect; low CO synd = low cardiac output syndrome; CHF = congestive heart failure; po = postoperative; cath = right heart catheterization; aneurysm OT = aneurysm of prosthesis in outflow tract.

in whom it was employed was 14.3 minutes with a range from 9.5 to 26 minutes. Mild total body hypothermia, from 29–34°C., was used in most cases to compensate for aortic run-off due to bronchial artery collateral circulation. In selected instances, hypothermia permitted a safe decrease in the perfusion rate which avoided excess return of blood to the operative field from bronchial collateral vessels.

Sclerotic fibrous tissue in the infundibulum was resected. With two exceptions, extensive resection of muscle in the infundibulum was avoided. In all cases except one muscular obstruction was overcome by roof expansion of the outflow tract with a plastic prosthesis. When valvular stenosis or pulmonary arterial hypoplasia was found, the ventriculotomy was extended into the main pulmonary artery with incorporation of the Teflon patch into this part of the incision. Valvular pulmonic stenosis was divided.

The same operative procedure was employed by the same surgeon and surgical team throughout the series.

Surgical Results

The early results from surgery were excellent in sixteen patients. Cyanosis disappeared promptly after operation and exercise tolerance improved markedly. An additional five patients had a less optimum result initially, but gradually achieved a satisfactory outcome. Congestive heart failure was a persistent problem in these patients but steadily improved in all. Two survivors have had reopening of the ventricular defect, but neither is symptomatic.

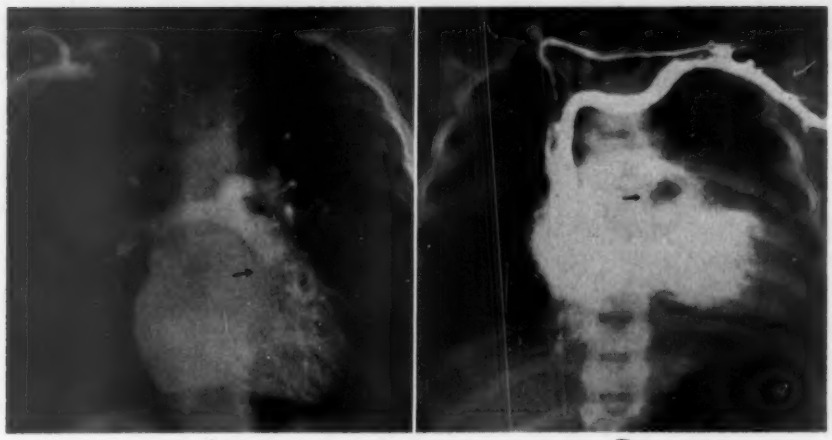
Four patients died during or soon after operation, an operative mortality of 14 per cent. One other patient died two months after surgery; the over-all mortality rate for the twenty-eight cases is 18 per cent.

Table II indicates that several patients who have had a satisfactory result from correction nonetheless had significant postoperative difficulties. In fact, only twelve patients had a totally uneventful course. The cardiovascular complications which occurred were of great significance in determining morbidity and mortality and will be discussed in detail.

Operative and Postoperative Complications

Heart Block

Persistent complete heart block with an idioventricular pacemaker occurred during cardiac exploration in one patient (Case 23). A satisfactory ventricular rate was provided by an electronic pacemaker with stimulation through myocardial wires which were placed



A B

FIG. 1. Angiograms displaying infundibular stenosis in its extremes. A, Case 9. A short segment of stenosis is present (arrow). B, Case 17. A tight, long segment of stenosis is apparent (arrow).

before bypass was discontinued. Normal rhythm returned after eight days.

Another patient (Case 26) had an episode of complete heart block during surgery which lasted only a few minutes. This recurred on the first postoperative day and percutaneous insertion of pacemaker wires was necessary. The heart rate was controlled and sinus rhythm returned a few days later.

Two other patients (Cases 11 and 19) had transient complete heart block during operation which persisted for a few minutes only and did not reappear. This occurred at a time unrelated to the immediate postarrest period.

In none of the cases was heart block permanent and it did not occur in any patient who died.

SYNDROME OF LOW CARDIAC OUTPUT

Measurements of cardiac output soon after open heart surgery have demonstrated that occasional patients will have an inadequate output, which is associated with a poor prognosis.[3] Metabolic acidosis may result although some degree of compensation is maintained by a high arteriovenous oxygen difference. The syndrome has been observed experimentally[4] and in patients who have had low perfusion rates or who have had inadequate correction of cardiac defects.[5–7]

Development of the syndrome of low cardiac output was a highly significant factor related to morbidity and mortality in our series. In its most severe form it was characterized by inability of the patient to maintain an adequate circulation following discontinuation of cardiopulmonary bypass. In other patients it was manifested by cardiogenic shock during the first forty-eight hours postoperatively. This consisted of peripheral vasoconstriction with cool skin and mild cyanosis, hypotension, increasing tachycardia and normal or slightly elevated venous pressure. The course in seven patients was complicated by this syndrome (Cases 14 to 20). These had tetralogy of varying degrees of severity, from pulmonary atresia to the acyanotic form.

Infundibular Muscular Resection: In two of the patients in this group the right ventricular wall was extremely thickened and the cavity was reduced to a slitlike chamber. In an attempt to relieve this obliterative hypertrophy, extensive muscular resection of the outflow tract was performed. In one (Case 17), the necessity for extensive resection was apparent in the preoperative angiocardiograms, which demonstrated a long segment of infundibular stenosis (Fig. 1). This patient was unable to maintain circulation whenever mechanical perfusion was stopped and he died after six hours of intermittent support with the pump oxygenator. In the other case (Case 14), complete preoperative evaluation including angiocardiography did not enable prediction of the need for radical infundibular resection. He had progressive deterioration during and after surgery with cyanosis, hypotension, metabolic acidosis, and he died. It is suggested that extensive resection of infundibular muscle greatly compromises right ventricular function, and that this is an important factor responsible for acute failure of the circulation after correction of tetralogy.

TABLE III
Pressures Obtained at Surgery by Needle Puncture (mm. Hg)

Case No.	Before Correction			After Correction		
	Right Ventricle	Infundibulum	Pulmonary Artery	Right Ventricle	Pulmonary Artery	Residual Systolic Gradient
1	90/0	...	18/8	28/2	25/7	3
2	120/18	35/10	30/20	34/11	35/14	0
3	115/8	50/10	15	60/12	35/12	25
4	100/8	84/8	15	32/10	...	...
5	95/0	30/5	30/17	34/14	...	...
6	...	...	...	42/13	45/10	0
7	120/20	45/5	22	38/12	25/20	13
8	105/5	40/10	40/10	35/17	32/24	3
9	70/10	13/5	...	50/10	...	...
10	87/10	...	25/12	42/12	40/18	2
11	85/5	80/5	12	65/10	25/10	40
12	100/12	25/12	17	47/5	28/12	19
13	97/8	43/8	25/10	33/8	25/10	8
14	...	...	...	46/8 to 112/40	12	34 to 100
15	100/10	...	13/8	40/5	13/8	27
16	90/5	85/5	14/5	70/15	38/17	32
17	100/35	50/20	25	38/7	...	...
18	125/15	120/15	27/17	40/12	26/12	14
19	105/10	33/15	30/15	43/11	43/15	0
20	110/15	65/15	8	75/20	35/20	40
21	77/5	35/5	13/5	50/7	40/12	10
22	125/8	...	14	52/10	32/13	20
23	102/10	110/20	11/6	43/7	42/16	1
24	100/10	40/10	12	45/10	15	30
25	105/5	32/10	30/10	30/8	...	...
26	125/12	125/12	30/15	60/10	32/11	28
27	115/5	25/2	12	37/8	30/12	7
28	87/10	77/10	10	55/10	10	45

Prolonged Cardiac Arrest: Another patient (Case 15) had a period of potassium citrate induced cardiac arrest which was unusually long for this clinic (twenty-six minutes). This is also the sole patient in the group who did not have an outflow tract prosthesis. A systolic gradient between the right ventricle and pulmonary artery was 27 mm. Hg after correction was completed. The patient had been doing well, but on the second postoperative day severe hypotension developed and he died despite treatment with norepinephrine and lanatoside C. Oligemia cannot be excluded as a contributing factor, and the persistent transpulmonic gradient may have been related. Recent reports[8,9] have described myocardial necrosis resulting from prolonged potassium arrest, although this was not present in the microscopic sections of the heart in this case. Reduced ventricular function following potassium arrest has been observed experimentally.[10] This, too, could have been a contributing cause for acute circulatory failure.

An unsatisfactory perfusion was the direct cause of death in another patient (Case 16). Metabolic acidosis developed during bypass and a large ileofemoral hematoma was discovered, resulting from a poorly functioning arterial cannula. Mild hypothermia to 30°C. was induced, and the arterial cannula changed to the other leg during a two minute period of total circulatory arrest. Surgery was further prolonged by difficulties in obtaining hemostasis and the patient died in the operating room. In this case, recovery was compromised by inadequate circulation during operation and a metabolic debt was produced which could not be reversed.

Postoperative Low Output Syndrome: A reversible low cardiac output syndrome developed postoperatively in three patients. This was noted immediately after surgery in one patient (Case 20) who had pulmonary atresia. A residual systolic gradient of 40 mm. across the infundibulum was measured in the operating room after correction, associated with a pulmonary artery pressure of 35/20 (Table III). The second patient (Case 19) had atresia of the left pulmonary artery and signs of poor cardiac output on the first postoperative day. Following correction, pressure in the main pulmonary artery was 43/15 and no residual pulmonic gradient was present. The third patient (Case 18) also had this syndrome on the first postoperative day. Her pulmonary arterial pressure after correction was 26/12 with a right ventricular pressure of 40/12 mm. Hg. These three patients received a trial of blood transfusion which effected no striking improvement. Vasopressor therapy was employed to maintain arterial pressure, and lanatoside C was given intermittently in large doses, although the patients had been digitalized preoperatively. All three recovered, although the syndrome persisted for forty-eight hours in Case 18. In contrast to those who died, metabolic acidosis did not develop.

It is of interest to speculate on the cause of the low cardiac output syndrome in the three patients who survived it. Two had pathologic anatomy different from any others in the series. One had pulmonary atresia. This patient (Case 20) had a significant residual pulmonic gradient which may have been a factor producing acute right ventricular failure. The moderate elevation of pulmonary artery pressure

after correction suggests either left ventricular failure or increased pulmonary vascular resistance as an additional mechanism. In the patient with atresia of the left pulmonary artery (Case 19), there was no residual gradient but pulmonary artery pressure was mildly elevated, suggesting the factors just mentioned. The third patient (Case 18) had a small residual gradient and a pulmonary arterial pressure within normal limits. Direct cardiac trauma, perfusion and induced cardioplegia of short duration seem unlikely as causes, in view of the inconsistency with which this syndrome appeared in the entire group of patients.

It would appear that early mortality and morbidity due to the low cardiac output syndrome may be related to extensive muscle resection in the infundibulum, unsatisfactory perfusion during bypass, prolonged cardiac arrest and a residual transpulmonic systolic gradient. The role of high pulmonary vascular resistance or left ventricular failure is uncertain; other unrecognized factors may be important as well.

CONGESTIVE HEART FAILURE

The long-term result of several features of the corrective operation are not yet known. These include the effects of the ventriculotomy and outflow tract prosthesis, the hemodynamic significance of pulmonic insufficiency which was produced in several patients, and the effects of a higher blood flow in the previously low flow pulmonary circuit. In addition, there is a change in the work pattern of the ventricles. Ventricular circulation in "parallel," with both sides contributing to systemic output, is changed to circulation in "series" by the repair. All of these factors were considered when congestive heart failure was observed in ten of the twenty-four patients surviving operation (Case 19 to 28). Others have noted the frequent development of temporary, late right ventricular failure after correction of tetralogy.[7]

Heart failure developed during the first week after surgery in three of these ten patients. In the remaining seven, the first evidence was found most often after ambulation on the ward had progressed for a day or two, during the second postoperative week.

In four patients in whom failure developed (Cases 22, 23, 27, 28), the manifestations were mild and consisted of slight enlargement and tenderness of the liver, venous distention and minimal tachypnea. With increased restriction of physical activity for a few days, more vigorous use of digitalis and other measures, the abnormality disappeared rapidly. These patients had a satisfactory surgical result.

Six patients had more severe and persistent congestive signs. In one (Case 25), the cause was reopening of the ventricular septal defect with obvious evidence of a large left to right shunt. The remaining five did not have signs of a residual shunt. Congestive failure eventually disappeared or was greatly improved in these, although amelioration occurred very gradually over a period of weeks to months. This progressive improvement justifies the optimistic view that failure will not be a recurrent problem. It is significant that no patient has died due to congestive failure.

Causes of Heart Failure: Examination of the causes of heart failure in 42 per cent of the patients who survived surgery is an important consideration in assessing the operative procedure. It is difficult to determine a single, consistent basis for this phenomenon. We have not observed a similar incidence of heart failure in patients operated on with cardiopulmonary bypass for other congenital lesions. It does not seem likely that bypass and perfusion are the direct causes for late and sometimes persistent failure. Myocardial trauma is not a reasonable sole explanation, as heart failure did not develop in the remainder of the survivors in this series although their operations were strikingly similar. The incidence of heart failure has been distributed throughout the period that the operations have been done. The duration of cardiac arrest was not different significantly in the failure and nonfailure groups. The ventriculotomy and outflow tract patch can be proposed as impairing ventricular function,[11] but once again all patients had these, whether or not failure developed. Two surviving patients (Cases 4 and 6) have evidence of a persistent ventricular defect but have had no signs of heart failure. It is reasonable to search for some additional hemodynamic load peculiar to those in whom heart failure developed, in addition to any of the aforementioned possibilities.

The outstanding differences in the patients with heart failure were the presence preoperatively of marked cyanosis or observation at surgery of a small pulmonary artery, or both. Eight of the ten patients with failure had pulmonary arteries found by the surgeon to be smaller than normal, though six of fourteen

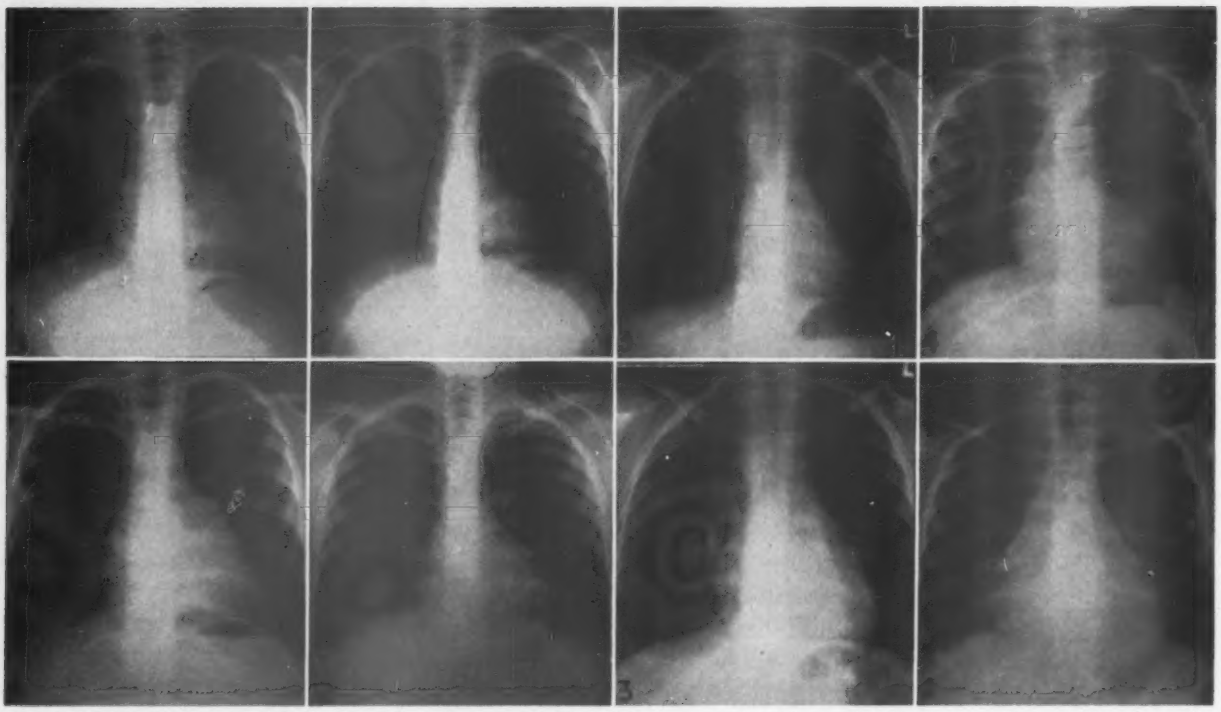


FIG. 2. Paired preoperative (top row) and postoperative (bottom row) radiographs illustrating the grades of cardiac enlargement. It should be emphasized that the grading is of changes in a given patient and not changes relative to normal findings. Grade 1, Case 3; grade 2, Case 13; grade 3, Case 26; grade 4, Case 20.

without failure also had this finding. Almost two-thirds of the failure group had hematocrits above 60 per cent, whereas only three of the fourteen others had similar values. Thus, *a small pulmonary artery or a high hematocrit* would appear to be predisposing factors, but not always so if only one or the other is present. However, in all surviving patients who had both a small pulmonary artery and a hematocrit of 60 per cent or more congestive failure developed postoperatively, without exception.

Importance of Small Pulmonary Artery and Restricted Pulmonary Vascular Bed: One might speculate concerning the relationship of the combination of marked cyanosis and small pulmonary artery to the development of heart failure. These two parameters are without doubt an indication of markedly diminished pulmonary blood flow. Since growth of a vascular tree may well depend on the volume of flow, it can be postulated that hypoplasia of the entire pulmonary arterial system is present in some of these patients. This may present a high resistance circuit when normal pulmonary flow results from correction. An alternative explanation is provided by the work of Rich[12] and of Ferencz[13] which showed a marked tendency for formation of thrombi in the pulmonary arteries in patients with tetralogy, with a propensity for recanalization of the organized thrombi. It is an attractive hypothesis that improvement in the protracted failure in some of our patients was related to the latter, since thrombotic lesions have been shown to disappear after restoration of more normal pulmonary flow.[14]

Pressure records were repeated at surgery after the heart was closed and stable rhythm present (Table III). These provide suggestive evidence for increased pulmonary vascular resistance. Twelve patients of the entire series had pulmonary arterial systolic pressures above 30 mm. Hg, with the highest being 45/10. Left atrial pressure and cardiac output are not known for this period, however, and thus definite conclusions cannot be drawn from the pulmonary artery pressures alone.

The patients with small pulmonary arteries posed more difficult surgical problems for alleviation of the right ventricular outlet obstruction. Three of the patients in the group with congestive failure had residual pulmonic systolic gradients from 30 to 45 mm. Hg and one in the group without failure had a residual gradient of similar magnitude. Pulmonic valvular insufficiency would be expected more often in those cases in which the ventriculotomy was extended upward into the pulmonary artery,

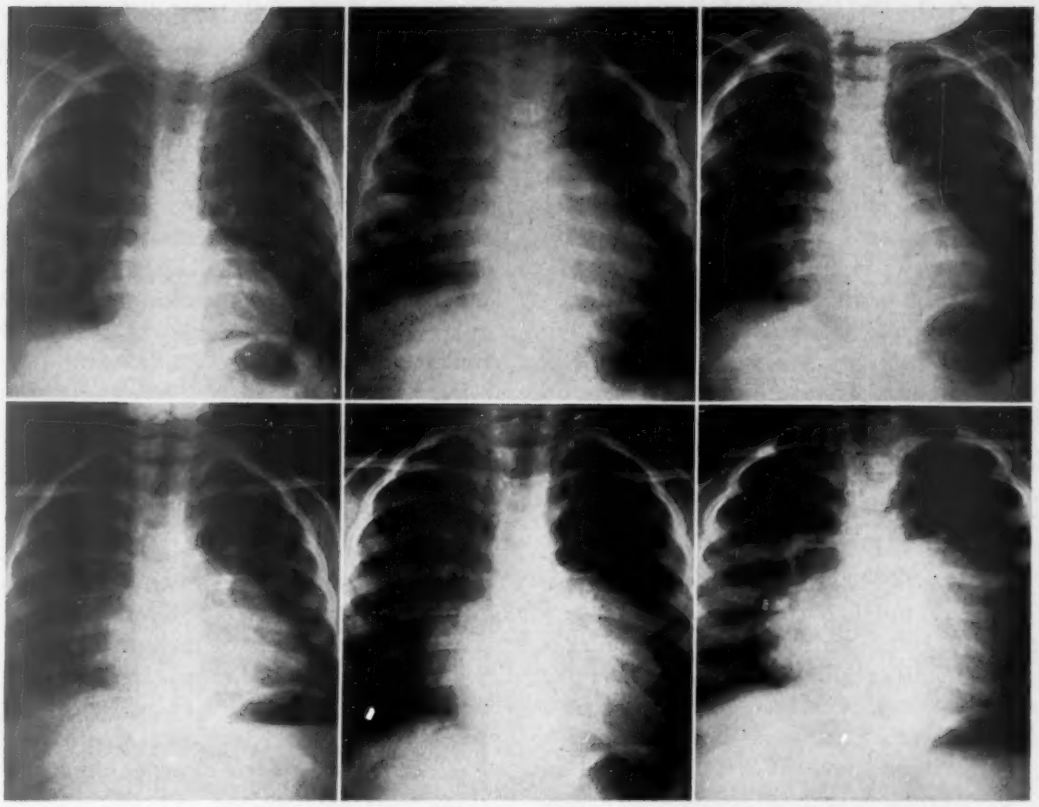


FIG. 3. Case 21. Radiographs illustrating the progressive aneurysmal dilatation of the right ventricular outflow tract. In this case alone, Ivalon rather than Teflon was employed for the outflow tract prosthesis. The film on the upper left was obtained before surgery.

which was done most often in those with small arteries. However, the observed incidence of pulmonic regurgitation murmurs postoperatively was not different in the groups with and without failure.

It is believed that tetralogy of Fallot is associated with restricted pulmonary vascular bed, and that with provision of higher pulmonary flow a significant hemodynamic burden remains for the right ventricle. Its efficiency is partly compromised by an incision and patch and a residual pulmonic gradient would contribute further to the work load. With time, pulmonary resistance lessens or ventricular function improves, or both occur, since failure disappears in nearly all cases. Whether or not an element of left ventricular failure is contributory is not known. Studies are in progress which are intended to elucidate this problem.

Postoperative Radiographs

The pre- and postoperative radiographs of the chest show that the cardiac silhouette increased in size in all but two of the twenty-four patients surviving surgery. Both patients who had no increase in cardiac dimensions were acyanotic and had cardiomegaly prior to surgery (Cases 5 and 8). Case 5, which had a proved left to right shunt preoperatively, showed a diminution in heart size to normal as well as reduction of pulmonary plethora.

Twenty-one of the twenty-two patients with increased cardiac size after surgery had cardiac silhouettes greater than normal limits. Although the cardiothoracic ratios were increased in the majority of these patients, these failed to give proper dimension to the changes. Therefore, this was arbitrarily graded as follows: grade 1, filling out of the right ventricular outflow tract or pulmonary arterial segment: grade 2, the previous finding and enlargement of the apex; grade 3, the aforementioned changes as well as enlargement of the right atrial shadow; and grade 4, massive enlargement of the heart in all dimensions. Four patients had grade 1 enlargement, eight had grade 2, seven had grade 3 and two had grade 4. Representative examples are shown in Figure 2.

The most striking change noted in the postoperative films was filling of the right ventricular outflow tract or pulmonary artery segment.

In the single patient (Case 21) in whom Ivalon was employed for the outflow tract prosthesis, progressive enlargement to aneurysmal proportion has been observed (Fig. 3). This has not occurred in any of the other cases.

Two patients had an increase of pulmonary vascularity to an abnormal degree. Both of these patients (Cases 4 and 6) were proved to have residual left to right shunts due to incomplete closure of the ventricular septal defect.

Only two patients (Cases 20 and 24) have shown a diminution of heart size during the period of follow-up. These were the two who manifested the most severe degree of heart failure postoperatively.

Postoperative Electrocardiograms

Right Bundle Branch Block: Postoperative electrocardiograms demonstrated an increase in the width of the QRS complex in all surviving patients when compared with preoperative records. The configuration was of right bundle branch block type and nine cases had a QRS duration of 0.12 second or more. A previous study[15] has shown that this conduction defect following the repair of ventricular septal defects is due to the location of the defect in relation to the conduction system, rather than to other factors such as ventriculotomy. The septal defect in tetralogy of Fallot is in the characteristic position of those which are associated with right bundle branch block after repair.

P Waves: Two-thirds of the patients whose postoperative electrocardiograms were available for study had a diminution in height of the P wave in lead II, although only six had preoperative evidence of P "congenitale." The cause for this is not certain, but it is of interest to consider a relationship to a decrease in right atrial pressure following relief of the pulmonic stenosis. Despite evidence of decrease in the magnitude of the P waves, there is an apparent increase in size of the right atrium after surgery, as determined by radiographs.

Management of Complications

Cardiovascular problems occurred in several patients postoperatively, as described. With vigorous treatment, patients with these complications usually will survive.

Heart Block: Persistent complete heart block occurring during surgery is managed best with the use of an electronic pacemaker and myocardial wires. This is preferable to attempts to maintain acceleration of an intrinsic pacemaker with sympathomimetic drugs. It is our practice to place pacemaker wires in the myocardium during surgery if heart block has been present at any time during the procedure for more than a minute or two, and especially if block has been recurrent during the operation. Though the pacemaker often is not needed postoperatively, it is available immediately for use should atrioventricular conduction fail again. Recurrent heart block occurred on the first postoperative day in one of our patients in whom wires had not been placed, and percutaneous insertion was required. This was successful, but prophylactic implantation during surgery would have been much easier and more dependable.

Low Cardiac Output: The syndrome of low cardiac output was amenable to treatment when not produced by overwhelming causes. The diagnosis rested in part on lack of improvement with blood transfusion. Norephinephrine and lanatoside C were the primary drugs employed. Though cardiogenic shock has not been uniformly accepted as an indication for digitalis, we believe that it is important in therapy of the syndrome herein discussed. We have seen this syndrome occur in undigitalized patients with an apparent response to administration of digitalis. In addition, increasing amounts of digitalis in digitalized patients in whom the syndrome developed has seemed efficacious on clinical grounds. Measurements of arterial blood pH, carbon dioxide content, and buffer base (by nomogram) were of aid in assessing the response to treatment. Those with progressive metabolic acidosis always failed to survive.

After the first few cases, all patients were digitalized preoperatively, because of the plan for a ventriculotomy. In addition, congestive heart failure after surgery was observed as experience increased, and preoperative preparation with digitalis was reasonable. Experimental and clinical evidence supports the prophylactic use of digitalis for open heart surgery[16,17] and it is planned to continue the practice for most patients having open cardiotomy in our hospital.

Congestive Failure: Heart failure was severe in some of the patients, but familiar therapeutic measures were successful in controlling it. Digitalis was used in large doses, and given to the point of tolerance. Restriction of salt intake was essential and mercurial diuretics were

helpful occasionally. An adequate period of bed rest was mandatory. All patients were kept in bed for the first postoperative week and then ambulated gradually. Because of the propensity for the development of congestive failure in these patients, activity has been curtailed longer than in those with other congenital defects following repair. In the more severe cases, activity was gradually increased over a period of months while the patients were at home.

Conclusions

Most patients with tetralogy of Fallot can be anatomically corrected by open heart surgery with an acceptable mortality risk. The immediate result is striking in many cases and the ultimate result is excellent in most. It is not yet known to what degree complete physiologic normality is approached by the results of surgical correction. Observation for a longer time is required, as well as careful hemodynamic study of such cases. Whatever long-term abnormalities persist, they are believed to be minimal, because of the marked clinical improvement which is evident, as well as the satisfactory progress of those with complicated courses.

Summary

An analysis of the postoperative course in twenty-eight patients who had complete correction of tetralogy of Fallot is presented. Pertinent preoperative findings are summarized and the operative procedure is briefly described.

During or following surgery, seven patients had a syndrome of low cardiac output, which was lethal in four. Factors which may have contributed to the development of this state are discussed.

The operative mortality rate was 14 per cent. One patient died during re-operation for persistence of the ventricular septal defect; the over-all mortality rate was 18 per cent.

Congestive heart failure developed in 42 per cent of surviving patients. This was transient in some and had a more protracted course in others. All patients recovered and late improvement was impressive. Possible mechanisms for this incidence of heart failure are presented.

The ultimate result from surgery was considered excellent in the majority of cases.

It is concluded that total correction is feasible in most patients with tetralogy of Fallot, with an acceptable surgical mortality.

References

1. Starr, A., Menashe, V, D., Bristow, J. D. and Griswold, H. E. Total correction of tetralogy of Fallot. Surgical technique and hemodynamic results. In preparation.
2. Starr, A. Oxygen consumption during cardiopulmonary by-pass. *J. Thoracic & Cardiovasc. Surg.*, 38: 46, 1959.
3. Boyd, A. D., Tremblay, R. E., Spencer, F. C. and Bahnson, H. T. Estimation of cardiac output soon after intracardiac surgery with cardiopulmonary by-pass. *Ann. Surg.*, 150: 613, 1959.
4. Litwin, M. S., Panico, F. G., Rubini, C., Harken, D. E. and Moore, F. D. Acidosis and lactic acidemia in extracorporeal circulation. *Ann. Surg.*, 149: 188, 1959.
5. Callaghan, J. C., Fraser, R. S., Dvorkin, J. and Stewart, A. G. The acid-base aspects of extracorporeal circulation. In: Extracorporeal Circulation, pp. 187, 188. Springfield, Illinois, 1958. Charles C Thomas.
6. Kolff, W. J., Effler, D. B. and Groves, L. K. A review of four dreaded complications of open-heart operations. *Brit. Med. J.*, 5180: 1149, 1960.
7. Lyons, W. S., DuShane, J. W. and Kirklin, J. W. Postoperative care after wholebody perfusion and open intracardiac operations. *J.A.M.A.*, 173: 625, 1960.
8. McFarland, J. A., Thomas, L. B., Gilbert, J. W. and Morrow, A. G. Myocardial necrosis following elective cardiac arrest induced with potassium citrate. *J. Thoracic & Cardiovasc. Surg.*, 40: 200, 1960.
9. Helmsworth, J. A., Kaplan, S., Clark, L. C., McAdams, A. J., Matthews, E. C. and Edwards, F. K. Myocardial injury associated with asystole induced with potassium citrate. *Ann. Surg.*, 149: 200, 1959.
10. Waldhausen, J. A., Braunwald, N. S., Bloodwell, R. D., Cornell, W. P. and Morrow, A. G. Left ventricular function following elective cardiac arrest. *J. Thoracic & Cardiovasc. Surg.*, 39: 799, 1960.
11. Stirling, G. R., Stanley, P. H. and Lillehei, C. W. The effects of cardiac bypass and ventriculotomy upon right ventricular function. *Surgical Forum*, 8: 433, 1957.
12. Rich, A. R. A hitherto unrecognized tendency to the development of widespread pulmonary vascular obstruction in patients with congenital pulmonary stenosis (tetralogy of Fallot). *Bull. Johns Hopkins Hosp.*, 82: 389, 1948.
13. Ferencz, C. The pulmonary vascular bed in tetralogy of Fallot. I. Changes associated with pulmonic stenosis. *Bull. Johns Hopkins Hosp.*, 106: 91, 1960.
14. Ferencz, C. The pulmonary vascular bed in tetralogy of Fallot. II. Changes following a systemic-pulmonary arterial anastomosis. *Bull. Johns Hopkins Hosp.*, 106: 100, 1960.
15. Bristow, J. D., Kassebaum, D. G., Starr, A. and

GRISWOLD, H. E. Observations on the occurrence of right bundle branch block following open repair of ventricular septal defects. *Circulation*, 22: 896, 1960.

16. BLOODWELL, R. D., GOLDBERG, L. I., BRAUNWALD, E., GILBERT, J. W., ROSS, J., JR. and MORROW, A. G. Myocardial contractility in man. *Surgical Forum*, 10: 532, 1959.
17. WILLMAN, V. L., COOPER, T. and HANLON, C. R. Prophylactic and therapeutic use of digitalis in open heart operations. *Arch. Surg.*, 80: 860, 1960.

Effect of the Application of Venous Tourniquets on Blood Volume*

PHILIP SAMET, M.D., F.A.C.C., WILLIAM H. BERNSTEIN, M.D., F.A.C.C. *and* ROBERT J. BOUCEK, M.D.

Miami Beach, Florida

BLOODLESS PHLEBOTOMY by means of rotating tourniquets applied to the extremities is commonly employed in the therapy of acute left ventricular failure. Experimental evidence that this procedure results in an altered blood volume is limited to five patients.[1] The purpose of this study is to investigate the effect of venous tourniquets on plasma volume and red cell mass in a large group of subjects.

METHODS AND MATERIALS

Forty-eight studies were performed in forty-three subjects. The vital statistics and diagnoses are listed in Table I. Most subjects were patients with cardiac disease who had previously had cardiac failure and were receiving digitalis and diuretics. A few had heart failure at the time of study. Some patients were studied more than once. No patient had pulmonary edema at the time of study.

Red cell mass and plasma volume were determined by P^{32} and T-1824 as previously described.[2] All patients were in the postabsorptive state after an overnight fast. Initial determinations of plasma volume and red cell mass were made after at least two hours in the supine position. Venous tourniquets were applied by wrapping five inch wide standard blood pressure cuffs about the upper thighs and arms as close to the trunk as possible. The cuffs were inflated to levels 5 to 10 mm. Hg below the diastolic arterial pressure levels. The duration of application of the venous tourniquets is listed in Table I. Repeated measurements of plasma volume and red cell mass were made via second (intraarterial) injections of P^{32} and T-1824 during the last thirty minutes of the indicated periods of tourniquet application. These latter values were corrected for the volumes of red cell and plasma volume removed during the first blood volume determination.

All samples for T-1824 and radioactive phosphorus determination were drawn via a Cournand indwelling arterial needle ten, twenty and thirty minutes after injection; the data were plotted on semilogarithmic paper to permit extrapolation to the zero time of injection. Arterial samples for T-1824 and P^{32} analysis were also drawn ten and twenty minutes after release of the tourniquets and plotted on the same semilogarithmic scale employed for plotting the data obtained during application of the tourniquets.

Rotating tourniquets were employed in twenty-five studies (Table IIA). The tourniquets were automatically rotated every ten minutes so that tourniquets were applied to any one extremity for thirty of each forty minute period. In twenty-three studies (Table IIB) nonrotating tourniquets were applied to three of the four extremities for periods of time and pressure levels indicated in Table I.

RESULTS

The data in the two groups of patients are listed in Tables IIA and IIB.

ROTATING TOURNIQUETS

The average initial plasma volume totaled 2,746 ml. (Table IIA). After application of rotating tourniquets, the uncorrected and corrected corresponding values were 2,663 and 2,745 ml., respectively. There is a statistically significant difference between the first two mean values (2,746 and 2,663 ml.) ($P < 0.01$, 95 per cent confidence limits -25 to -141 ml.). The first and third mean plasma volumes (2,746 and 2,745 ml.) are not significantly different ($1 > P > 0.9$, 95 per cent confidence limits $+56$ to -58 ml.). The corresponding red cell mass data were 1,660 (control), 1,540 (uncorrected) and 1,592 (corrected) ml., respectively. There is a statistically significant difference between the first two means ($P< 0.001$, 95 per cent confidence limits -78 to -161 ml.), and between the first and third means ($P < 0.01$, 95 per cent

* From the Cardio-Pulmonary Laboratory and the Department of Medicine, Mount Sinai Hospital, Miami Beach, and the Section of Cardiology of the Department of Medicine, University of Miami School of Medicine, Coral Gables, Florida. Supported by a research grant from the National Heart Institute [H-2436 (C3)] and from the Heart Association of Greater Miami.

TABLE I
Diagnoses and Rotating Tourniquet Data

Case No.	Age (yrs.) and Sex	Body Surface Area (sq. M.)	Diagnosis*	Tourniquet	
				Duration (hrs.)	Pressure † (mm. Hg)
1	50, M	1.89	Rh HD, EH, MS, AF, CHF, IIIE	3½	60 (R)
2	60, M	1.61	As HD, cor pulmonale, EH, AF, CHF, IIID	3½	60 (R)
3A	48, M	1.80	Cor pulmonale, EH, NSR, IIIC	3½	60 (R)
B		1.81	(In failure during study 3B)	1⅔	65 (R)
C		1.80		1	70 (NR)
4	55, F	1.61	Rh HD, EH, MI, NSR, CHF, IIID	2½	60 (R)
5	51, F	1.77	Rh HD, EH, MI, MS, AF, IIIC	3	60 (R)
6A	59, F	1.56	Cong HD, EH, IA defect, AF, CHF, IIIC	1½	75 (R)
B		1.52		1	45 (NR)
7	40, F	1.61	Rh HD, EH, MS, NSR, IB	1½	75 (R)
8	66, M	1.67	Rh HD, EH, AS, AI, NSR, IIIC	2	65 (R)
9	32, F	1.53	Rh HD, EH, MS, AI, AS, NSR, IIC	1½	65 (R)
10	44, F	1.56	Idiopathic dilation, pul art, IA	1½	65 (R)
11	52, F	1.55	Rh HD, EH, MI, MS, NSR, IIIC	1⅔	55 (R)
12	34, M	1.90	Rh HD, EH, MS, MI, NSR, IB	1½	70 (R)
13	41, F	1.61	Rh HD, EH, TS, MS, MI, AF, IIIC	1	65 (R)
14	50, F	1.77	Rh HD, EH, MI, MS, AI, AF, IIIC	1⅔	50 (R)
15	48, F	1.58	Rh HD, EH, MI, MS, AF, IIIC	1⅔	60 (R)
16A	39, F	1.45	Rh HD, EH, MS, NSR, IIIC	2	60 (R)
B		1.43		1⅔	60 (R)
17A	34, M	2.01	Rh HD, EH, AS, AI, NSR, IIC	2	65 (R)
B		2.01		1	60 (NR)
18	54, M	1.28	Cor pulmonale, EH, NSR, CHF, IIID	1½	60 (R)
19	63, M	1.32	Cor pulmonale, EH, NSR, IIIC	1½	60 (R)
20	43, M	1.73	Rh HD, EH, MS, MI, AF, IIIC	1⅔	60 (R)
21	38, M	1.94	Rh HD, EH, MI, MS, AI, IIIC	1½	50 (R)
22	39, F	1.45	Rh HD, EH, AI, AS, NSR, IIC	1⅔	55 (R)
23	38, M	1.73	Cong HD, EH, ductus arteriosus, NSR, IIC	1	50 (R)
24	49, M	2.00	Carcinoma left lung	1	60 (NR)
25	48, M	2.08	Cor pulmonale, EH, NSR, IIC	1	60 (NR)
26	35, M	2.22	Rh HD, EH, MS, NSR, IB	1	55 (NR)
27	41, M	1.76	Rh HS, EH, AS, AI, NSR, IB	1	45 (NR)
28	26, F	1.53	Rh HD, EH, MI, MS, AF, IIC	1⅓	60 (NR)
29	48, M	2.05	Unknown HD, EH, AF, IIC	1	65 (NR)
30	52, M	1.86	Polycythemia vera	1	65 (NR)
31	58, M	2.18	Cor pulmonale, EH, NSR, IIIC	1	60 (NR)
32	46, M	1.67	Rh HD, EH, AI, NSR, IIIC	1	50 (NR)
33	73, M	1.81	Cor pulmonale, EH, NSR, IIIC	1	60 (NR)
34	60, M	1.97	Cor pulmonale, EH, NSR, IIC	1	60 (NR)
35	62, M	1.51	Cor pulmonale, EH, NSR, IIIC	1	65 (NR)
36	50, M	1.84	Cor pulmonale, EH, ST, IIIC	1	65 (NR)
37	46, M	1.72	Rh HD, EH, AS, AI, NSR, IIC	1	50 (NR)
38	54, M	1.63	As HD, EH, NSR, LBBB, IIIC	1	60 (NR)
39	74, M	1.63	Cor pulmonale, EH, ST, IIID	1	65 (NR)
40	21, F	1.94	Normal	1	60 (NR)
41	27, F	1.54	Repaired IA septal defect	1	46 (NR)
42	33, F	1.46	Rh HD, EH, MS, MI, NSR, IIIC	1	50 (NR)
43	41, F	1.52	Rh HD, EH, MS, NSR, IB	1	60 (NR)

* Rh HD = rheumatic heart disease; EH = enlarged heart; MS = mitral stenosis; MI = mitral insufficiency; TS = tricuspid insufficiency; AS = aortic stenosis; AI = aortic insufficiency; IA = interatrial; NSR = normal; AF = atrial fibrillation; CHF = congestive heart failure; As HD = arteriosclerotic heart disease; Cong HD = congenital heart disease; Unknown HD = heart disease of unknown etiology; LBBB = left bundle branch block.

† R = rotating tourniquets; NR = nonrotating tourniquets.

TABLE II

Plasma Volume and Red Cell Mass before and during Tourniquet Application

Case No.	Plasma Volume Analysis (ml.)				Red Cell Mass Analysis (ml.)				Arterial Hematocrit (× 0.96)		Body Hematocrit	
	Initial Determination	Second Determination	Volume Removed between Analyses	Corrected Volume	Initial Determination	Second Determination	Volume Removed between Analyses	Corrected Volume	Initial Determination	Second Determination	Initial Determination	Second Determination
A. Rotating Tourniquets (four limbs)												
1	4,299	4,291	89	4,380	2,212	2,020	51	2,071	36.2	35.6	33.9	32.0
2	3,399	3,211	84	3,295	2,027	1,842	56	1,898	41.7	41.3	37.3	36.4
3A	3,087	3,141	77	3,218	2,120	1,985	63	2,048	43.7	44.6	40.7	38.7
B	3,311	3,249	79	3,328	2,258	1,894	61	1,955	43.4	39.6	40.5	36.8
4	2,713	2,717	85	2,802	1,564	1,464	55	1,519	39.2	38.7	36.6	35.0
5	3,025	2,934	86	3,020	1,608	1,503	54	1,557	37.6	38.4	34.7	33.8
6	3,346	3,215	87	3,302	1,808	1,643	53	1,696	37.9	36.2	35.1	33.8
7	1,912	1,807	93	1,900	900	894	47	941	33.5	34.2	32.0	33.0
8	2,727	2,567	87	2,654	1,542	1,422	53	1,475	37.4	39.2	36.0	35.6
9	1,908	1,741	87	1,828	1,053	1,007	53	1,060	38.0	38.7	35.5	36.6
10	2,389	2,254	90	2,344	1,152	1,112	50	1,162	35.7	35.9	32.5	33.0
11	2,214	2,282	90	2,372	1,231	1,061	50	1,111	35.9	35.6	35.7	31.7
12	2,681	2,768	84	2,852	1,815	1,662	56	1,718	40.0	40.5	40.2	37.5
13	2,836	2,375	87	3,562	1,626	1,341	53	1,394	37.8	39.5	36.4	36.0
14	3,415	3,396	78	3,474	1,865	1,752	52	1,804	37.8	35.0	35.3	34.0
15	2,812	2,470	80	2,550	1,638	1,306	52	1,358	37.3	37.0	36.8	34.5
16A	2,268	2,314	84	2,398	1,104	993	46	1,039	34.0	32.9	32.7	30.0
B	2,050	2,000	78	2,078	1,035	952	49	1,001	35.9	36.6	33.5	32.2
17	3,638	3,298	78	3,376	2,375	2,343	49	2,392	41.6	44.3	39.4	41.5
18	1,727	1,737	79	1,816	1,467	1,410	49	1,459	48.1	49.0	45.9	44.8
19	1,507	1,614	73	1,687	1,314	1,242	46	1,288	47.2	48.1	46.5	43.3
20	2,930	2,903	78	2,981	1,716	1,688	51	1,739	38.0	38.9	36.9	36.8
21	4,121	4,121	71	4,192	2,456	2,382	54	2,436	41.1	38.5	37.3	36.6
22	2,007	1,917	74	1,991	1,198	1,286	51	1,337	41.6	42.5	37.3	40.1
23	2,353	2,252	78	2,330	2,458	2,350	53	2,403	53.7	54.0	51.1	51.1
Average	2,746	2,663	82	2,745	1,660	1,540	52	1,592	39.8	39.8	37.6	36.6
B. Nonrotating Tourniquets (three limbs)												
3C	3,122	2,995	75	3,070	2,538	2,307	47	2,354	50.2	49.5	44.8	43.5
6B	3,116	3,120	78	3,198	1,728	1,567	50	1,617	38.2	36.4	35.8	33.4
17B	3,348	3,081	74	3,115	2,547	2,555	54	2,609	44.8	45.2	43.2	45.3
24	3,271	3,260	78	3,338	2,233	1,996	50	2,046	39.6	40.3	40.5	37.9
25	2,943	2,788	74	2,862	2,188	2,205	47	2,252	46.3	46.2	42.7	44.2
26	3,335	3,235	78	3,313	2,062	1,960	50	2,010	39.8	40.3	38.1	37.7
27	2,543	2,427	80	2,507	1,653	1,473	51	1,524	41.8	42.2	39.4	37.8
28	2,562	2,384	78	2,462	1,422	1,278	50	1,328	37.6	38.8	35.7	34.9
29	3,217	3,124	81	3,205	2,631	2,621	47	2,668	46.6	47.8	45.0	45.6
30	2,569	2,209	78	2,287	2,259	2,139	50	2,189	51.1	52.5	46.7	49.1
31	3,841	3,751	80	3,831	2,516	2,595	51	2,646	42.0	42.8	39.6	40.9
32	2,768	2,442	80	2,522	1,774	1,556	47	1,603	39.8	40.5	39.1	38.9
33	3,242	2,989	75	3,064	3,536	3,161	50	3,211	54.0	54.0	52.2	51.4
34	3,475	3,387	78	3,465	1,852	1,719	47	1,767	37.5	38.3	34.8	33.7
35	2,147	2,135	71	2,206	1,982	1,806	50	1,856	49.8	49.5	48.0	45.8
36	3,059	2,853	79	2,932	2,076	2,079	52	2,131	44.3	44.6	40.4	42.2
37	2,487	2,281	75	2,356	1,904	1,754	50	1,804	44.3	44.4	43.3	43.5
38	2,833	2,639	79	2,718	2,186	1,917	49	1,966	43.5	44.2	43.6	42.1
39	2,254	2,000	77	2,077	1,825	1,650	54	1,704	48.8	49.9	44.7	45.2
40	2,572	2,466	79	2,545	1,246	1,157	50	1,207	33.6	34.2	32.6	31.9
41	2,214	2,140	80	2,220	1,160	1,079	49	1,128	35.5	35.5	34.3	33.5
42	2,141	2,078	78	2,156	1,170	1,100	50	1,150	38.0	38.5	35.3	34.6
43	1,881	1,888	71	1,959	869	781	48	829	32.8	33.0	31.6	29.4
Average	2,820	2,680	77	2,757	1,973	1,845	50	1,896	42.5	43.0	40.5	40.1

confidence limits −27 to −108 ml.). The change in arterial hematocrit values after application of the tourniquet was not significant ($1 > P > 0.9$, 95 per cent confidence limits −0.60 to +0.64). The decrease in body hematocrit value was significant ($0.01 > P > 0.001$, 95 per cent confidence limits −0.30 to −1.69).

NONROTATING TOURNIQUETS

The average control plasma volume equaled 2,820 ml. (Table IIB). After application of nonrotating tourniquets, the uncorrected and corrected corresponding values were 2,680 and 2,757 ml., respectively. There is a statistically significant difference between the first two

mean values ($P < 0.001$, 95 per cent confidence limits −98 to −187 ml.), and between the first and third means ($0.01 > P > 0.001$, 95 per cent confidence limits −20 to −109 ml.). The corresponding red cell mass data were 1,973 (control), 1,845 (uncorrected) and 1,896 (corrected) ml., respectively. There is a statistically significant difference between the first two mean values ($P < 0.001$, 95 per cent confidence limits −81 to −172 ml.), and between the first and third mean values ($0.01 > P > 0.001$, 95 per cent confidence limits −31 to −122 ml.). The change in arterial hematocrit is of limited significance ($0.02 > P > 0.01$, 95 per cent confidence limits +0.08 to +0.68). No significant change in body hematocrit was noted ($0.3 > P > 0.2$, 95 per cent confidence limits −1.02 to +0.25).

The P^{32} and T-1824 data obtained ten and twenty minutes after release of the tourniquets fell on the same semilogarithmic straight line extrapolation as did the points obtained during tourniquet application.

Comments

The data obtained in the present study demonstrate a fall in red cell mass after application of both rotating and nonrotating venous tourniquets, before and after correction for the red cell mass removed between the two determinations. The maximum average decrease in red cell volume is about 130 ml. uncorrected for the red cell volume removed, and about 80 ml. after such correction is made. The maximum decrease in plasma volume after application of the tourniquet is 140 ml. uncorrected and 65 ml. corrected (Table IIA and B). The maximum decrease in total blood volume after the application of tourniquets is, therefore, about 270 ml. uncorrected and 145 ml. corrected (Table IIA and B). These decreases in total blood volumes constitute only about 5 per cent of the total blood volumes noted in these subjects.

Seven studies (Cases 1, 2, 4, 6, 3B, 18, 6B) in six patients were performed while the subjects had heart failure. The first six such determinations were done with rotating tourniquets. The average uncorrected and corrected decrease in red cell mass was 177 and 123 ml., respectively. The average uncorrected fall in plasma volume was 62 ml.; when corrected, the plasma volume actually increased 21 ml. The data from the single patient with heart failure studied with nonrotating tourniquets were similar (Table IIB, Case 6B). The blood volume alterations induced by venous tourniquets are, therefore, of similar magnitude in patients with compensated and decompensated cardiac disease.

Failure of the post-tourniquet release P^{32} and T-1824 points to fall below the straight line extrapolation of the corresponding points obtained during tourniquet application indicates that little or no P^{32} and T-1824 free fluid was added to the vascular bed in the post-tourniquet period.

These data are at variance with those obtained by Ebert and Stead.[1] Employing a different experimental protocol, they found that venous tourniquets placed on three extremities at diastolic pressure levels in five patients removed 720 ml. of blood from the head, trunk and arm. This volume of blood "represented 15 per cent of the volume of blood normally circulating in the head, trunk and arm." These observations were made employing T-1824 to measure plasma volume; red cell mass was not measured directly. The authors concluded that "this investigation demonstrated that as much blood was removed from the general circulation by venous tourniquets as by the usual phlebotomy." The text of their paper further states, "It is significant that a measurable amount of fluid is lost from the bloodstream during the period of venous engorgement. This is in part the result of the increased capillary pressure. More fluid would have been lost if the period of congestion had been prolonged. This loss of fluid from the bloodstream explains in part the clinical observation that in the treatment of acute left ventricular failure the beneficial effects of tourniquets persist for some time after their release." Their Figure 1 shows that "plasma volume is decreased after the release of tourniquets and has not completely returned to normal at the end of twenty minutes." The quantitative, but not qualitative, difference in the data of Ebert and Stead and those in the present study is probably due to the larger number of subjects employed in the present study.

Altschule[3] has reviewed the evidence relative to the hemodynamic effect of venous tourniquets. Peters[4] demonstrated that there is a loss of fluid from the blood into the tissues of the limbs to which the tourniquets were applied with a consequent increase in plasma specific gravity or hemoglobin concentration. Landis[5] showed that the swelling of the limb after venous congestion persisted for a time after removal of the tourniquet. The data in the present study demonstrate only a small decrease in plasma

volume after application of venous tourniquets.

In view of the small decrements in blood volume after application of venous tourniquets noted in these forty-eight experiments, a question must be raised as to the mechanism of the clinical improvement observed in patients with acute left ventricular failure treated with venous tourniquets. It is unlikely that removal of even 250 ml. of blood could *per se* result in the pronounced beneficial effect of "bloodless phlebotomy" in patients with pulmonary edema. A decrease in cardiac output has not been uniformly observed after tourniquets were applied for venous congestion.[6–9]

Measurements of true volume of pulmonary blood, as recently performed by Milnor, Jose and McGaff,[10] may provide a clue to the mechanism of clinical improvement. These investigators determined central blood volumes via systemic arterial sampling after injection of indocyanine green into the pulmonary artery and into the left atrium in the course of combined right and left heart catheterization. The difference between these two "central blood" volumes is defined as the volume of pulmonary blood. If all or most of the small decreases observed in total blood volume after application of venous tourniquets were secondary to decreases in true volume of pulmonary blood, a more satisfactory explanation for the therapeutic effect of bloodless phlebotomy would be at hand. Hamilton and Morgan[11] have observed that application of venous tourniquets results in an increase in vital capacity even in normal subjects in the dorsal recumbent position. Studies are planned to provide the necessary direct data of the effect of venous tourniquets on true volume of pulmonary blood.

Vascular collapse with hypotension developed in several subjects treated with venous tourniquets. Other investigators[2,12] have had similar experiences, pointing to the need for careful observation of the patient during the use of tourniquets.

Summary

Rotating and nonrotating venous tourniquets were applied to the extremities at pressure levels of 5 to 10 mm. Hg below the diastolic blood pressure in twenty-five and twenty-three studies, respectively. This procedure resulted in only modest decreases in plasma volume and red cell mass, totaling less than 5 per cent of the total blood volume. Similar results were obtained in subjects studied during congestive heart failure (but not acute pulmonary edema) and in patients with compensated cardiac disease.

The physiologic mechanism responsible for the clinical improvement noted with application of venous tourniquets in acute left ventricular failure is, therefore, uncertain. Several alternative mechanisms remain to be evaluated.

References

1. Ebert, R. V. and Stead, E. A., Jr. The effect of the application of tourniquets on the hemodynamics of the circulation. *J. Clin. Invest.*, 19: 561, 1940.
2. Samet, P., Fritts, H. W., Jr., Fishman, A. P. and Cournand, A. The blood volume in heart disease. *Medicine*, 36: 211, 1957.
3. Altschule, M. D. Physiology in Disease of the Heart and Lungs, p. 321. Cambridge, 1954. Harvard University Press.
4. Peters, J. P., Jr., Bulger, G. A., Eisenman, A. J. and Lee, C. Total acid-base equilibrium of plasma in health and disease. IV. The effects of stasis, exercise, hyperpnea, and anoxemia; and the causes of tetany. *J. Biol. Chem.*, 67: 175, 1926.
5. Landis, E. M., Jonas, L., Angevine, M. and Erb, W. The passage of fluid and protein through the human capillary wall during venous congestion. *J. Clin. Invest.*, 11: 717, 1932.
6. Howarth, S., McMichael, J. and Sharpey-Schafer, E. P. Effects of venesection in low output heart failure. *Clin. Sc.*, 6: 41, 1946.
7. Fitzhugh, F. W., Jr., McWhorter, R. L., Jr., Estes, E. H., Jr., Warren, J. V. and Merrill, A. J. The effect of application of tourniquets to the legs on cardiac output and renal function in normal human subjects. *J. Clin. Invest.*, 12: 1163, 1953.
8. Warren, J. V., Brannon, E. S., Stead, E. A., Jr. and Merrill, A. J. The effect of venesection and the pooling of blood in the extremities on the atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances. *J. Clin. Invest.*, 24: 337, 1945.
9. Judson, W. E., Hollander, W., Hatcher, J. D., Halperin, M. H. and Friedman, I. H. The cardiohemodynamic effects of venous congestion of the legs or of phlebotomy in patients with and without congestive heart failure. *J. Clin. Invest.*, 34: 614, 1955.
10. Milnor, W. R., Jose, A. D. and McGaff, C. J. Pulmonary vascular volume, resistance, and compliance in man. *Circulation*, 22: 130, 1960.
11. Hamilton, W. F. and Morgan, A. B. Mechanism of postural reduction in vital capacity in relation to orthopnea and storage of blood in lungs. *Am. J. Physiol.*, 99: 526, 1932.
12. Fuchs, L. Ueber die Messung des Venendruckes und ihre klinische Bedeutung. *Deutches Arch. f. klin. Med.*, 68: 135, 1921.

Experimental Studies

Experimental Roentgenologic Visualization of Normal and Abnormal Coronary Arteries*

WILLIAM H. SEWELL, M.D.,† WADE H. SHUFORD M.D. *and* PABLO A. DAVALOS, M.D.

Atlanta, Georgia

FURTHER PROGRESS in the field of surgery for coronary arterial disease will probably be dependent upon a satisfactory method for the roentgenologic visualization of the coronary arteries, just as successful widespread application of surgery for occlusive arterial disease in the extremities was dependent upon the development of the technics for arteriography of the extremities.

Several approaches to the problem of coronary arteriography have been used, and have been well reviewed by Lehman[1,2] and others. The purpose of this study is to compare several technics for visualization of these vessels in dogs.

METHODS USED

OCCLUSION AORTOGRAPHY

This method consists of brief occlusion of the ascending aorta by an inflatable rubber bag on a catheter, and injection of media proximally. This technic has been performed successfully in animals by Cannon[3] and Dotter and Frische.[4]

Technic: In the current series, dogs were anesthetized with pentobarbital sodium and endotracheal respiration initiated. The carotid artery was approached through a midline incision in the neck. A No. 8 double lumen cardiac catheter with a small inflatable rubber balloon on the end was inserted into this vessel. The tip was placed about 1 cm. above the aortic valve under fluoroscopic control. The balloon was inflated with air, and immediately thereafter 10 cc. of Thorotrast® was injected through the main lumen into the ascending aorta proximal to the occlusion. A single exposure was made using the Bucky grid.

Results: This technic resulted in moderately good filling of the major coronary arteries and secondary branches. It was performed on four normal dogs without mortality or evidence of myocardial damage, except for transient electrocardiographic changes.

Disadvantages: Although this technic has appeared satisfactory in normal dogs, it would probably be undesirable and perhaps unacceptable for human use. The geometric factors related to the larger size of the human patient would compound the difficulties of keeping the balloon in place in the ascending aorta, as was experienced by Frische and Dotter.[5] Successful application would probably require a rather rigid tube leading down to it, which would increase the danger of perforation of the aortic arch during insertion.

This procedure was not tested on hearts of dogs with myocardial infarction, but on theoretic grounds would be expected to be poorly tolerated. Likewise, a heart verging on congestive failure would probably be seriously damaged. Therefore, a procedure requiring occlusion of the ascending aorta does not appear to be a promising solution to the problem.

DIRECT THORACIC AORTOGRAPHY

Direct thoracic aortography has been the subject of numerous studies, and these have been well reviewed by Dotter and Frische.[4]

* From the Division of Thoracic Surgery of the Joseph B. Whitehead Department of Surgery, Emory University School of Medicine and Grady Memorial Hospital, Atlanta, Georgia. Supported by a grant from the Georgia Heart Association.

† Present address: Veterans Administration Hospital, Oteen, North Carolina.

This approach depends upon the very rapid injection of a relatively large quantity of contrast medium into the ascending aorta through a large catheter. Good results have been obtained by Richards and Thal[6,7] in both animals and human beings. They found that accurate timing of the injection in relation to the cardiac cycle permitted better visualization of the coronary arteries with less contrast material. Urschel and Roth[8] established early diastole as the optimal time for injection, by using very small amounts of medium. The equipment necessary to do this, however, is expensive and complicated. Good results have also been obtained by Bellman et al.,[9] using a catheter with a loop just above the aortic valve.

Technic: A series of experiments on six dogs was performed by the following technic: A No. 10 NIH catheter was inserted through a carotid artery into the ascending aorta and positioned immediately above the valve, using a fluoroscope. This catheter has a very large lumen in proportion to its total diameter and the end is closed. Several side holes are present in the area immediately adjacent to the end. A pneumatic pressure syringe was employed to inject 25 cc. of 85% Hypaque®* in about a half second. Exposures were made at the rate of six per second, using the Elema roll-film serial changer. The technical factors were 1000 ma. and 1/200 second exposure time at about 80 kv.p.

Results: The results in a normal dog are seen in Figure 1. Satisfactory filling of the coronary arteries was consistently obtained, with visualization of all major and secondary branches. There was consistent filling of tertiary branches believed to be about 300 μ in diameter, judging from measurements of comparable vessels in corrosion casts.

Advantages and Disadvantages: This technic (rapid injection, six films per second, and a short exposure time) has the major advantage of requiring no reduction of the cardiac output. Visualization was as good as that obtained by any other method. A disadvantage is the fact that more contrast material must be used than would be necessary if elective cardiac arrest were performed. Although careful coordination of the injection with the cardiac cycle would obviously decrease the amount necessary, it would probably not reduce it to the levels which are adequate when arrest is used.

* Supplied by Winthrop Laboratories.

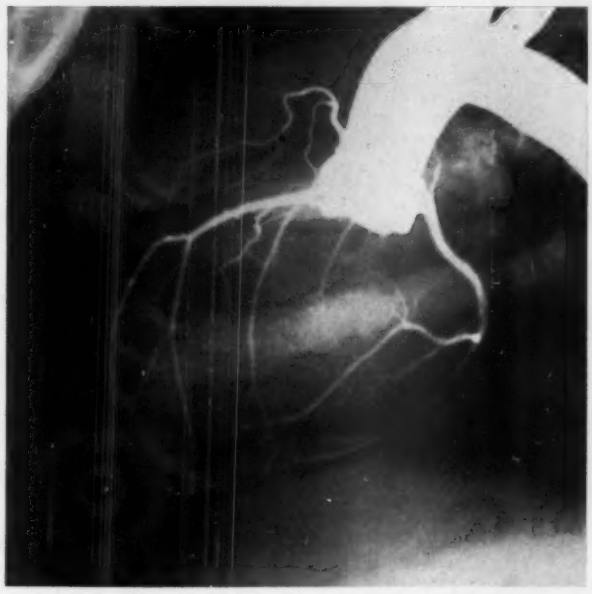


FIG. 1. Coronary arteriogram of a normal dog in lateral position, obtained without the use of cardiac arrest at 1/200 second exposure time.

Several dogs tolerated 75 cc. of 85% Hypaque as the total used in three injections. However, one dog which received 100 cc. died, apparently from this very high dose of contrast medium.

ELECTIVE CARDIAC ARREST

Transient elective cardiac arrest as a method for permitting visualization of the coronary arteries has been considered by Lehman,[1] Anlyan et al.,[10,11] Arnulf,[12] and others. After communication with Dotter this method was evaluated in a series of dogs.

Technic: The carotid artery was exposed as before and a No. 10 NIH catheter was inserted into the proximal aorta. The best position for the tip was found to be about 1 cm. above the aortic valve. The dog was paralyzed with succinylcholine and ventilated with a respirator. From 2 to 5 mg. of acetylcholine in 10 cc. of saline were injected through the catheter. Immediately thereafter 10 cc. of 85% Hypaque was injected by hand.

If the contrast medium was not injected promptly after the arrest, the aortic valve was likely to open and permit regurgitation into the left ventricle. The electrocardiogram was continuously recorded, and in many dogs the aortic pressure was recorded through the femoral artery (Fig. 2).

Forty-two arrests were performed in sixteen normal dogs. In all cases the heart stopped within a second after injection of the acetyl-

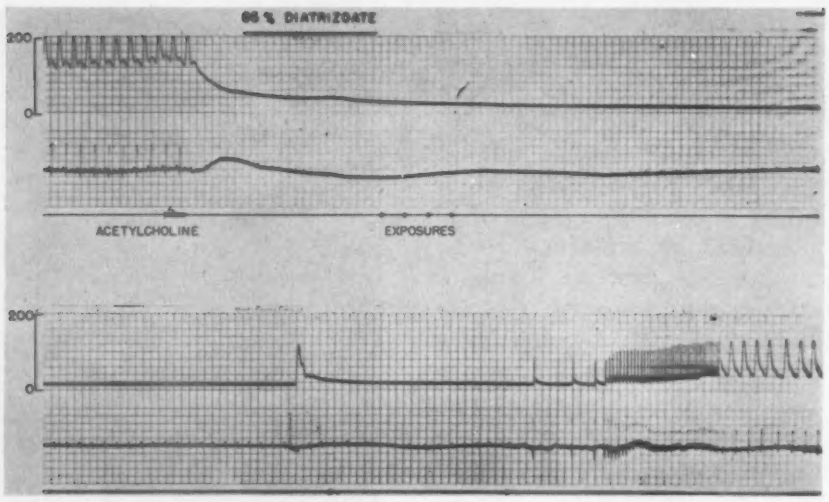


Fig. 2. Femoral arterial pressure and lead II recorded during temporary cardiac arrest with acetylcholine, injection of contrast media, x-ray exposure and spontaneous return of cardiac rhythm.

choline. Asystole lasted for an average of about twenty seconds. P waves sometimes returned before the QRS complexes. The first few beats were likely to be characterized by a widened and abnormal QRS and a markedly distorted S-T segment and T wave. Twelve-lead electrocardiograms taken after several minutes showed little or no change from the control tracings. The femoral arterial pressure usually rose to a level somewhat above the control and returned to it after several minutes. No ectopic beats were encountered in any of the normal animals.

Films were taken on a Fairchild serial roll-film device at the rate of two per second, for about two seconds. A delayed exposure was usually made immediately after the first ventricular contraction. The technical factors were 200 ma., $^1/_{20}$ of a second exposure time and 70–80 kv.p.

Results: Excellent visualization of the coronary arteries was obtained in all of fifty-five consecutive attempts with this method (Fig. 3). The major, secondary and tertiary branches were well visualized. The detail was, in general, slightly better than that which could be obtained by injection without arrest referred to previously. In none of the normal dogs was any collateral arterial circulation demonstrated.

Advantages and Disadvantages: This method has the advantage of requiring a relatively small amount of contrast material. It gives very reliable and satisfactory results in dogs, and can be done with rather readily available equipment.

The obvious disadvantage is the psychologic and perhaps the physiologic hazard of elective arrest. Although the necessity did not arise in any of the dogs used, the heart should have been responsive to an external pacemaker, because acetylcholine primarily depresses the ability of the heart to initiate an impulse rather than the ability of the myocardium to respond to stimulus.

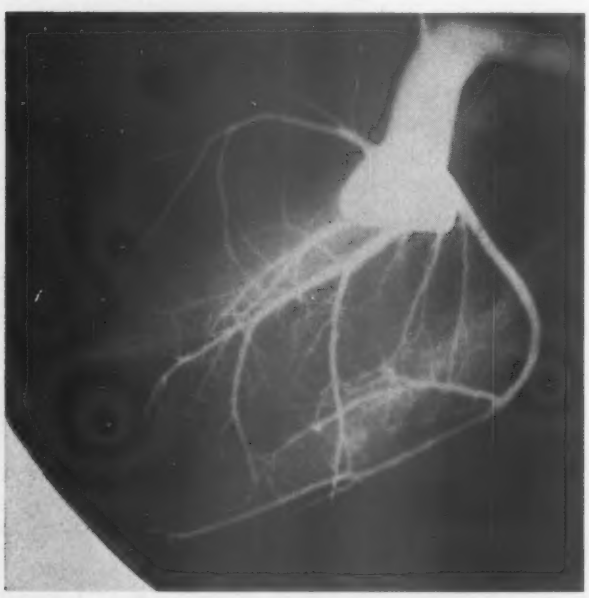
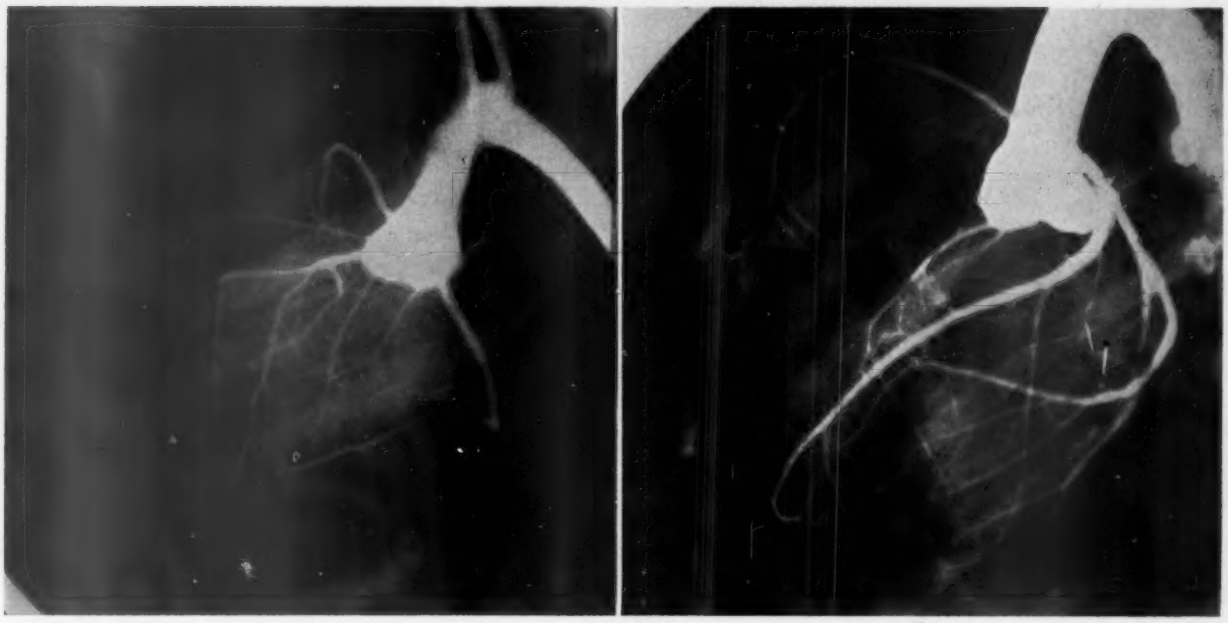


Fig. 3. Coronary arteriogram of a normal dog, obtained during transient cardiac arrest with acetylcholine.

CINEARTERIOGRAPHY

Cinearteriography permits demonstration of the sequence of events which occurs during coronary arteriography with and without arrest.



A B

Fig. 4. A, coronary arteriogram obtained with the use of acetylcholine arrest technic three weeks after ligation of the anterior decending artery near its midpoint. Collateral channels have formed around the apex. B, coronary arteriogram taken in left anterior oblique position, using cardiac arrest. A constriction by copper wire on the left main coronary artery is demonstrated (arrow).

The preceding injections were repeated and 16 mm. movies were made at fifteen and thirty frames per second. A Picker 5-inch image amplification unit was used. This study showed that the degree of coronary arterial filling with and without arrest is comparable.

The cinefluorographic technic did not give as detailed visualization of the small vessels, but permitted fluoroscopy without moving the subject and required less expensive film.

Arteriography in Abnormal Dogs

Further experiments were done on abnormal dogs in order to explore the capacities and limitations of the method of acetylcholine arrest for coronary arteriography. Furthermore, studies are necessary to enable correct interpretation of the roentgenologic pattern of normal coronary arteries, partial occlusions, complete occlusions and the presence of collateral arterial communications. A series of experiments were done on dogs with various types of occlusions or constrictions of the coronary arteries.

In some dogs, the anterior descending coronary artery was ligated in its midportion. The point of occlusion of the anterior descending is demonstrated in Figure 4A, taken three weeks after the surgical procedure. Both the point of occlusion and collateral arterial channels can be demonstrated.

In another series, constrictions of copper wire were placed around the left main coronary artery proximal to the origin of the anterior descending, circumflex and septal branches. This point of constriction usually cannot be demonstrated in the standard lateral films, because of superimposition on the ascending aorta. The left main coronary artery can be regularly demonstrated, however, by use of an extreme left anterior oblique projection, as seen in Figure 4B. No collateral channels were noted around the apex in this series, unless the trifurcation was such that the wire impinged upon the anterior descending artery at its origin.

Safety of Experimental Cardiac Arrest

A total of twenty-eight arteriograms using elective cardiac arrest were performed on eleven abnormal dogs. Of these, two arrests were done on dogs with induced thrombosis of the anterior descending artery. Nine were done on dogs with complete ligation of the vessel near its midportion. Eight were done on dogs with a constriction of the anterior descending and four were on those with constriction of the left main coronary artery. Three arrests were done on a dog with congenital patent ductus arteriosus in congestive heart failure with tachycardia and cardiac enlargement. Two were done on a dog with a

surgically created left to right shunt at the atrial level. After three arrests, all of the hearts spontaneously resumed a normal rhythm in all instances, except for two.

One dog had two abnormal ventricular contractions but then normal rhythm developed. This dog had a moderately severe myocardial infarct. Another dog had ventricular fibrillation after the second arrest during the same anesthesia. No resuscitation was attempted. This heart was found to be extensively infarcted, as a result of ligation of the anterior descending artery four months previously. The dog had tolerated three elective cardiac arrests for arteriography two weeks after surgery, without arrhythmia.

There were two unsuccessful attempts to obtain arteriograms early in the series. The thoracic aorta was perforated with a polyethylene catheter. This did not occur with the NIH catheter.

Comments

Single exposures can be used if the arrest technic is employed, but multiple films are sometimes desirable. The latter permitted demonstration of the progression of contrast media through collateral channels, thereby establishing the direction of flow through them.

Catheters with a closed end and side openings have been compared to those with open ends. Those with closed ends were found to be most satisfactory. An open end results in a jet effect, which extends for a somewhat unpredictable distance and direction, requiring placement of the catheter higher in the aortic arch in order to avoid frequent regurgitations through the aortic valve. Reliable filling of the coronary arteries is more difficult to obtain. Furthermore, a catheter with side openings does not recoil very much during high speed injection, whereas this may be a serious problem with the other type.

Summary

This project was designed to compare the reliability, safety and adequacy of detail of several methods for demonstrating roentgenologically the smaller branches of the coronary arterial tree in dogs.

Reasonably good results were obtained using occlusion of the ascending aorta by a bag on a catheter. This method is believed, however, to be more difficult and dangerous than other technics.

Good visualization was obtained using 25 cc. of 85% Hypaque injected mechanically through a catheter in the ascending aorta, without altering the cardiac output. This technic required $^1/_{200}$ of a second exposure and six films per second in order to give satisfactory results.

Acetylcholine arrest was the simplest and most satisfactory technic for the animals. It could be done with single films and $^1/_{20}$ of a second exposure. No arrhythmias occurred in normal dogs, but ventricular fibrillation and death resulted during one of twenty-eight arrests in dogs with surgically created coronary arterial disease.

Cinefluorography using a 5-inch image amplification unit and 16 mm. film provided a good demonstration of the sequence of events occurring in arrest and nonarrest technics. The detail was definitely inferior to that obtained with direct x-ray film exposure.

References

1. Lehman, S. Coronary arteriography: practical considerations. *Progr. Cardiovas. Dis.*, 2: 36, 1959.
2. Lehman, S., Boyer, R. A. and Winter, F. S. Coronary arteriography. *Am. J. Roentgenol.*, 81: 749, 1959.
3. Cannon, J. A. L. Accurate diagnostic coronary arteriography in the dog. *Surg. Forum*, 6: 197, 1956.
4. Dotter, C. T. and Frische, L. H. Visualization of the coronary circulation by occlusion aortography: a practical method. *Radiology*, 71: 502, 1958.
5. Frische, L. H. and Dotter, C. T. An improved method of coronary arteriography. *Dis. Chest.*, 35: 546, 1959.
6. Richards, L. S., and Thal, A. Phasic dye injection control system for coronary arteriography in the human. *Surg. Gynec. & Obst.*, 107: 739, 1958.
7. Richards, L. S., Greenspan, R. H. and Thal, A. A comparative study of diastolic and systolic dye injection in human coronary arteriography. *Surg. Forum*, 9: 237, 1959.
8. Urschel, H. C., Jr. and Roth, E. J. Electronically controlled coronary arteriography. *Ann. Surg.*, 150: 275, 1959.
9. Bellman, S., Frank, H. A., Lambert, P. B., Littman, D. and Williams, J. A. Coronary arteriography. I. Differential opacification of the aortic stream by catheters of special design; experimental development. *New England J. Med.*, 262: 325, 1960.
10. Anlyan, W. G., Baylin, G. J., Fabrikant, J. I. and Trumba, R. T. B. Studies in coronary angiography. *Surgery*, 45: 8, 1959.
11. Fabrikant, J. I., Anlyan, W. G., Baylin, G. J. and Trumba, R. T. B. A comparison of techniques for visualization of the coronary arteries. *Am. J. Roentgenol.*, 81: 764, 1959.
12. Arnulf, G. Systemic coronary arteriography with acetylcholine cardiac arrest. *Prog. Cardiovas. Dis.*, 2: 197, 1959.

A Study of Predominance of Human Coronary Arteries Determined by Arteriographic and Perfusion Technics*

JOHN S. VASKO, M.D., JOHN GUTELIUS, M.D. *and* DAVID C. SABISTON, JR., M.D.

Baltimore, Maryland

THE ANATOMY of the coronary arteries has recently been re-emphasized in association with the use of diagnostic coronary arteriography. Coronary endarterectomy for angina pectoris and the preoperative identification of significant coronary anomalies in various types of congenital cardiac lesions have also stressed the importance of the roentgenographic demonstration of the coronary vessels. The classic pathologic and radiologic studies in the literature indicate that "right coronary predominance" is the most common pattern of distribution and is followed in incidence by a "balanced" and least frequently by a "left coronary predominant" circulation. These observations are essentially *anatomic* ones and much less is known about the *physiologic* relationship of the volume of blood which normally flows through each of the coronary arteries. In the present study experiments were designed to compare arteriographic and perfusion data in the determination of coronary artery predominance in the human heart.

METHODS

Fifty-six human hearts of subjects ranging in age from 7 to 93 years were studied at the time of postmortem examination. In all instances hearts without acute cardiac disease were used. Of the hearts examined, thirty-two were normal and twenty-four had cardiac disorders of various types (Table 1). The proximal portions of both coronary arteries were isolated in each heart with care to avoid interruption of any small branches. A polyethylene catheter with a flanged tip was introduced into each coronary ostium and tied in place with a silk ligature. Particular attention was taken to place the tip of the catheter as close to the origin of the coronary ostium as possible to prevent occlusion of small branches originating near the aorta.

Coronary arteriograms were performed using a concentrated solution of sodium iodide. Approximately 6 cc. was injected into each coronary artery and roentgenograms were obtained with the heart in the anteroposterior and lateral positions.

A *perfusion apparatus* was constructed and attached to a mercury manometer and a constant pressure source (Fig. 1). The heart was immersed in a saline bath maintained at 37°c. and the coronary cannulae were connected to the perfusion system. The coronary circulation was flushed initially with 200 cc. of saline at 37°c. Forty-six hearts (85 per cent) were perfused at a mean pressure of 100 mm. Hg. The remaining eight hearts were perfused at an average pressure of 150 mm. Hg (range of 120 to 240 mm. Hg). Two hearts were not perfused because of leaks in the coronary arteries.

Determination of Coronary Predominance: An adaptation of the criteria used by Schlesinger[1] was employed in the *arteriographic* determination of coronary arterial predominance. In this classification the arterial supply to the *crux* of the heart is basic in the differentiation of "right predominant," "left predominant" and "balanced" hearts. The "crux" is defined as the point on the posterior surface of the heart at which the left and right ventricles, the left and right atria and the interatrial and interventricular septa meet. The basic variable in coronary arterial supply under these circumstances is the reciprocal relationship between the length of the left circumflex coronary artery and the right coronary artery. Either one or both of these arteries may extend to the *crux* of the heart and it is at this point that the posterior descending coronary artery has its origin. This vessel may arise from either the right or left circumflex arteries or from both. If the right coronary artery crosses the *crux* posteriorly and supplies a portion of the left side of the heart, the heart is considered "right predominant" by arteriog-

* From the Department of Surgery, The Johns Hopkins University School of Medicine and Hospital, Baltimore, Maryland. This work was aided by a grant (H-2864) from the National Heart Institute, National Institutes of Health, United States Public Health Service, Bethesda, Maryland.

TABLE I

Comparison of Coronary Predominance by Arteriographic and Perfusion Studies

Status	No. of Hearts	Arteriogram Predominance			Perfusion Predominance		
		Right	Left	Balanced	Right	Left	Balanced
Normal	32	15	7	10	5	23	4
Cardiac disease*	24	12	2	10	5	13	2
Total	56	27 (48%)	9 (16%)	20 (36%)	10 (19%)	36 (69%)	6 (12%)

* Cardiac diseases include: hypertensive cardiovascular disease (15); arteriosclerotic cardiovascular disease (9).

TABLE II

Coronary Artery Flow Values during Perfusion in Normal Hearts

Case No.	Age and Sex	Weight (gm.)	Coronary Flow* (cc. sal./min.)		Arteriogram Predominance
			Right	Left	
1	7, M	120	50	42	Right
2	12, M	240	50	108	Left
3	17, M	280	48	104	Left
4	18, F	280	40	88	Balanced
5	18, M	270	92	95	Left
6	20, M	290	84	143	Right
7	21, F	300	112	79	Right
8	22, M	270	26	81	Left
9	35, M	280	30	51	Balanced
10	41, F	290	88	87	Right
11	42, F	300	57	44	Right
12	46, F	210	35	141	Balanced
13	46, F	220	68	82	Right
14	48, M	240	55	59	Right
15	48, F	270	36	99	Balanced
16	54, M	370	70	60	Balanced
17	54, M	450	75	112	Right
18	54, F	300	40	50	Balanced
19	60, F	210	37	71	Left
20	60, F	290	49	67	Right
21	61, F	250	38	157	Right
22	62, F	340	89	185	Right
23	65, M	370	22	169	Left
24	65, M	350	54	92	Balanced
25	66, M	270	60	90	Right
26	67, F	370	102	157	Right
27	67, M	350	84	120	Balanced
28	70, M	...	52	45	Right
29	70, F	380	23	148	Left
30	71, M	480	133	212	Balanced
31	75, F	350	103	223	Balanced
32	77, M	340	46	70	Right

* All were perfused at 100 mm. Hg pressure.

raphy. When the left circumflex coronary artery crosses the crux to the right side of the heart it is considered "left predominant." The hearts in which both the right and left coronary arteries reach the crux and do not cross it in a definite fashion are considered "balanced."

The designation of *perfusion predominance* is based simply on the quantitative volume flow through each coronary artery per unit of time. If the volume flowing through the left coronary artery exceeded that which flowed through the right in the same period of time, the heart was considered "left predominant" and vice versa. The "balanced" heart had essentially equal flows in both the right and left coronary arteries per unit of time. These criteria are employed in the definitions used in the present study.

RESULTS

The arteriograms showed that twenty-seven hearts were of the "right predominant" type (48 per cent), twenty had a "balanced" circulation (36 per cent) and nine were "left predominant" (16 per cent) (Table I). An example of a typical coronary arteriogram from each group is seen in

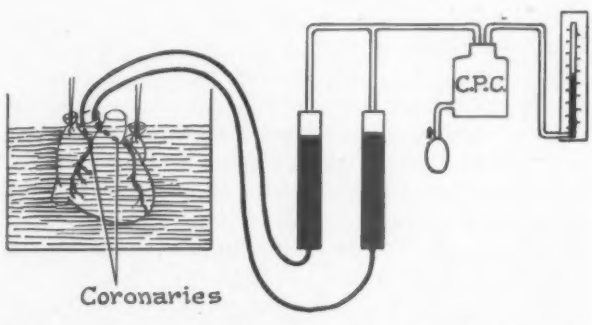


FIG. 1. Diagrammatic illustration of the method employed for perfusion of the coronary circulation. CPC represents the constant pressure chamber. (See text for description of details.)

TABLE III

Coronary Artery Flow Values during Perfusion of Hearts with Known Disease

Case No.	Age and Sex	Weight (gm.)	Perfusion Pressure (mm. Hg)	Coronary Flow (cc. sal./min.)		Arteriogram Predominance
				Right	Left	
			A. Arteriosclerotic Cardiovascular Disease			
1	58, M	320	100	26	81	Balanced
2	60, M	450	...	Not perfused	...	Balanced
3	65, M	400	100	71	73	Right
4	71, M	380	100	75	39	Balanced
5	77, M	570	100	10	177	Right
6	79, F	350	120	45	33	Right
7	84, F	270	100	8	41	Left
8	84, M	450	100	48	52	Right
9	93, M	500	100	72	95	Balanced
			B. Hypertensive Cardiovascular Disease			
1	28, F	470	150	114	124	Right
2	37, M	500	100	60	149	Right
3	39, M	450	...	Not perfused	...	Balanced
4	40, M	360	100	124	52	Balanced
5	42, F	520	150	156	128	Right
6	45, M	400	100	19	48	Right
7	47, F	360	170	132	136	Right
8	48, M	600	100	44	178	Balanced
9	58, F	390	150	59	118	Right
10	58, M	700	240	172	240	Balanced
11	59, M	730	150	69	132	Balanced
12	66, M	500	100	16	163	Balanced
13	67, M	550	100	13	218	Left
14	72, F	500	100	94	68	Right
15	81, F	...	170	99	188	Right

Figure 2. The perfusion studies provided an additional means of classification based upon the volume of saline which could be perfused through each of the coronary arteries at a constant pressure. The actual flow values during coronary arterial perfusion are shown in Tables II and III. The results of these perfusions showed thirty-six to be "left predominant" (69 per cent), ten to be "right predominant" (19 per cent) and six to be "balanced" (12 per cent) (Table I).

In relating the perfusion and roentgenographic findings it was noted that in seven of the eight hearts in which the arteriogram showed left predominance, the perfusion studies also confirmed a pattern of left coronary predominance. Fifteen of the eighteen hearts which were "balanced" on arteriography were noted also to be left preponderant by perfusion studies. In the group of twenty-six hearts which were right predominant at the time of arteriography, fourteen were found to be "left predominant" and seven "right predominant" at the time of perfusion with the remaining five being "balanced" (Table IV).

The average coronary flows in each of the three *arteriographic* groups provide some interesting comparisons. In the group of hearts which were *left* coronary predominant on the arteriogram, the right coronary flow represented an average of 31 per cent of the left coronary flow. In hearts which were balanced on arteriogram the right coronary arterial flow was 58 per cent of the flow on the left side. The hearts which showed right coronary arterial predominance on coronary arteriogram had a right coronary arterial flow which was 79 per cent of the value obtained for left coronary flow.

The average coronary arterial perfusion values in those hearts from patients with known arteriosclerotic cardiovascular disease were noted to be 40 per cent less than the average perfu-

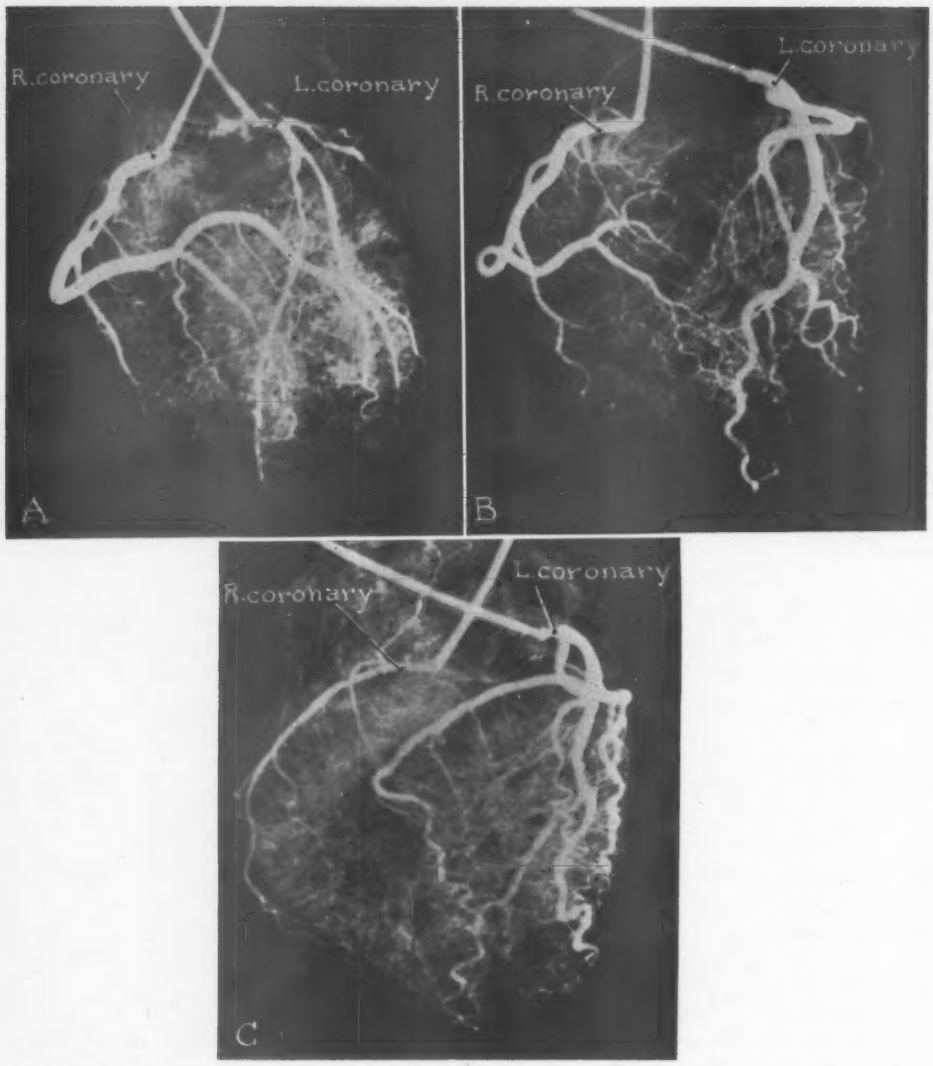


FIG. 2. Coronary arteriograms of human hearts representing a typical example of each anatomically predominant group. A, "right coronary predominant" heart; B, "balanced" heart; C, "left coronary predominant" heart.

sion values obtained from all other hearts. Hearts from patients with other cardiac diseases, principally hypertensive cardiovascular disease, had average coronary arterial flow values essentially the same as those hearts from normal persons.

COMMENTS

The criteria introduced by the outstanding work of Schlesinger and associates[1,2] for the determination of coronary arterial predominance have been used in a variety of studies. With the advent of clinical coronary arteriography and direct surgical procedures upon the coronary vessels, these criteria have assumed a new and greater significance. In the present studies the classification of Schlesinger has been employed in the intact heart injected with radiopaque media at the time of postmortem examination. Other investigators[3,4] have applied these criteria to coronary arteriograms obtained in living subjects with some degree of success.

By direct measurement Gregg[5] demonstrated that the left coronary artery is nearly always predominant in the dog. Measurement of the volume of coronary flow showed that approximately 85 per cent of the arterial supply to the myocardium was through the left coronary artery. There are no direct measurements available of individual flows in the right and left coronary arteries of the human heart. It is apparent, however, that the flow through these vessels varies in different subjects depending upon the anatomic patterns. In the past there

TABLE IV
Relationship of Coronary Perfusion to Arteriographic Predominance

Status	Balanced Arteriogram			Left Predominant Arteriogram			Right Predominant Arteriogram		
	Right Perfusion Predominant	Left Perfusion Predominant	Balanced Perfusion	Right Perfusion Predominant	Left Perfusion Predominant	Balanced Perfusion	Right Perfusion Predominant	Left Perfusion Predominant	Balanced Perfusion
Normal	4	8	3	0	6	1	1	9	0
Cardiac disease	3	6	2	0	1	0	2	6	0
Total	7 (27%)	14 (54%)	5 (19%)	0	7 (88%)	1 (12%)	3 (17%)	15 (87%)	0

has been considerable clinical evidence that the left coronary artery is functionally the more important and the inference has been that it conducts more blood to the myocardium. This concept has been substantiated by the observation that isolated perfusion of the left coronary artery at the time of open heart surgery is associated with better myocardial function than is isolated perfusion of the right coronary artery.[6] The correlation between the volume of coronary arterial flow and the radiologic demonstration of coronary arterial predominance has not been previously determined. In the present study on postmortem specimens, there appears to be little relationship between the perfusion and radiologic data. The marked preponderance of hearts with left coronary flows which are greater than right coronary flows indicates that the amount of muscle mass supplied by the two vessels may be important in the determination of predominance. In only 19 per cent of specimens did the volume of flow through the right coronary artery exceed that in the left coronary artery.

It should be emphasized that there are definite technical limitations in the perfusion of the myocardial vascular bed at the time of postmortem examination, and care must be taken in the interpretation of the data. The normal physiologic controls[7] which affect coronary blood flow in the normal heart are greatly altered, although the alterations are probably essentially the same for each of the hearts studied. In a group of recent experimental observations in our laboratory it has been noted that the volume of saline which may be perfused through the coronary arteries of the isolated dog heart is essentially normal immediately following removal from the chest. However, there is a gradual diminution in the amount which may be perfused through the coronary arteries at identical pressures with the passage of time. These studies have shown that 5 hours after death the volume which may be perfused at the same pressure through the coronary circulation is approximately one-fifth that which was perfused immediately after removal of the heart from the animal.[8] Furthermore, this decline is a gradual one. Therefore, it appears that the interval of time which has elapsed since death is an important determinant of the volume of flow which will pass through the coronary vascular bed. Of particular importance in the present study is the fact that the experimental data for the dog heart showed that a plateau is reached after approximately 5 hours. In the human hearts comprising the present study virtually all were perfused more than 5 hours after death.

SUMMARY

Coronary arterial predominance in the human heart has been studied at the time of postmortem examination by *arteriographic* and *perfusion* technics. A high incidence of right coronary predominance was demonstrated by coronary arteriography (48 per cent). Coronary arterial perfusion studies in the same hearts revealed a different pattern of coronary arterial predominance, showing 69 per cent of the hearts to be *left* coronary predominant, 19 per cent *right* coronary predominant and 12 per cent "balanced."

ACKNOWLEDGMENT

We are grateful to Dr. William M. Shelley, Resident in Pathology, for his cooperation in this study.

References

1. Schlesinger, M. J. Significant variations in the anatomic pattern of the coronary vessels. *A.A.A.S.*, 13: 61, 1940.
2. Schlesinger, M. J. An injection plus dissection study of coronary artery occlusions and anastomosis. *Am. Heart J.*, 15: 528, 1938.
3. Di Guglielmo, L. and Guttadauro, M. A roentgenological study of the coronary arteries in the living. *Acta radiol., suppl.*, 97: 1, 1952.
4. Di Guglielmo, L. and Guttadauro, M. Anatomic variations in coronary arteries. Arteriographic study in living subjects. *Acta radiol.*, 41: 393, 1954.
5. Gregg, D. E. The Coronary Circulation in Health and Disease, p. 78. Philadelphia, 1950. Lea and Febiger.
6. Muller, W. H., Jr., Warren, W. D., Dammann, J. F., Jr., Beckwith, J. R. and Wood, J. E., Jr. Surgical relief of aortic insufficiency by direct operation on the aortic valve. *Circulation*, 21: 587, 1960.
7. Sabiston, D. C., Jr. and Blalock, A. Physiologic and anatomic determinants of coronary blood flow and their relationship to myocardial revascularization. *Surgery*, 44: 406, 1958.
8. Vasko, J. Unpublished observations.

New Method

The Electrocardiogram during Exercise as Recorded by Radioelectrocardiography

Comparison with the Postexercise Electrocardiogram (Master Two-Step Test)*

SAMUEL BELLET, M.D., F.A.C.C., STAVROS DELIYIANNIS, M.D. *and* MARCEL ELIAKIM, M.D.

Philadelphia, Pennsylvania

MOST of the rather extensive literature on the effects of exercise on the electrocardiogram deals with the postexercise period. Few data are available relative to the electrocardiogram during the actual period of exercise. These include isolated reports of the data obtained by telemetering apparatus[1–6] as well as the conventional electrocardiograph.[7,8] In the latter case a special electrode placement was used, and interference due to muscle activity was filtered.

The object of this study is to report our experience with the electrocardiogram taken during the performance of exercise and its comparison with that obtained during the postexercise period. The method for recording the electrocardiogram during exercise is termed "radioelectrocardiography."[4–6] It utilizes a device which is similar to, but much simpler than, the usual telemetering apparatus available. The absence of a cable connection between the subject and the recording machine permits the performance of exercise at a maximal distance of 500 feet from the recording apparatus.

The records obtained with this method show a steady and stable baseline. The tracing is faithfully recorded during various forms of activity. The apparatus is simple; it can be easily applied for use in a doctor's office or in a hospital.

METHODS AND MATERIALS

This radioelectrocardiograph system† is based on the principle of radiobroadcasting the electrocardiogram, using a lightweight ratio transmitter worn by the patient. The apparatus (Figs. 1 and 2) utilizes specially designed disposable electrodes which easily adhere to the patient's skin; a 10 ounce pocket-sized, battery-operated radio transmitter, which can be worn by the patient; and a portable desk-model receiver which transmits the characteristic electrocardiographic waves to conventional recording equipment.

Electrodes and Their Placement: The electrode consists of a patch-type adhesive bandage with an electrode paste reservoir, a metallic screen and contact snap fastener. It is easily secured in place on the skin in a manner similar to applying most adhesive-type bandages. Measuring only $1^1/_2$ by $1^1/_2$ inches, these lightweight, disposable electrodes easily comply with the surface motion of the skin and help to deliver an accurate electrocardiographic signal (Fig. 3). Optimal results for the purpose of this study were obtained when the electrodes were placed at the fifth interspace on the right and left mid-axillary line, respectively (Fig. 4). The placement corresponds reasonably well to the unipolar lead V_6. This site is relatively free of muscle interference except during extreme exertion. Other sites of electrode placement may be employed; these may be varied, depending on the muscle movement in the types of

† RKG *100* is made by Telemedics Inc., Southampton, Pennsylvania (a subsidiary of Vector Manufacturing Company, Inc.).

* From the Division of Cardiology, Philadelphia General Hospital, Philadelphia, Pennsylvania, and the Division of Cardiovascular Disease, Graduate Hospital of the University of Pennsylvania.

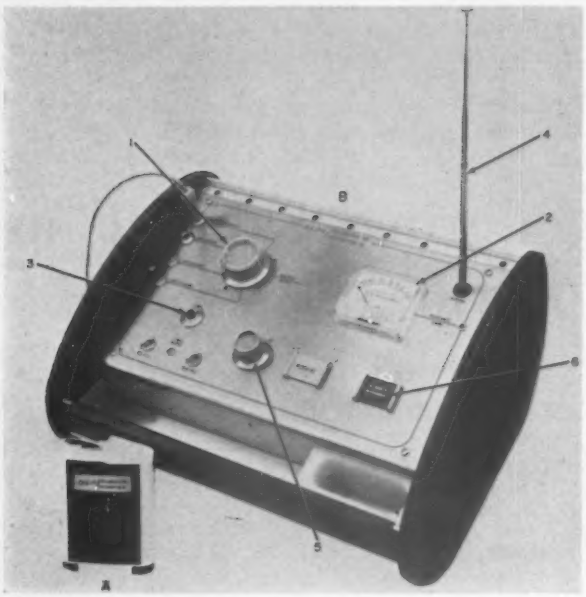


FIG. 1. Radio transmitter (A) and receiver (B). The radio transmitter (1 by 3 by 4 inches, weight 10 ounces) has only one contact for wires coming from the electrodes. The radio receiver has: (1) channel selector switch for channeling the electrocardiographic signals to (a) conventional electrocardiograph (connected in the figure), (b) oscilloscope and (c) tape recorder and tape playback; (2) skin resistance meter; (3) 1 mv. calibration; (4) collapsible antenna; (5) "on" and "off" switch; and (6) automatic recharger (the transmitter is placed into the suitably adjusted space shown on the lower right of the receiver).

exercise employed. Additional leads or other physiologic data may be recorded and transmitted simultaneously with a two- or three-channel recorder.

*The Radio Transmitter:** The frequency-modulated radio transmitter measures approximately 1 by 3 inches and is $4^1/_2$ inches high. It weighs 10 ounces including the batteries (Fig. 1). Input signals from the electrodes are carried by the thin flexible wires to the transmitter where they are amplified and transmitted from an antenna included in the transmitter itself. The batteries used to supply power to the circuits are self-contained, and of a rechargeable type capable of operating for continuous periods, up to five hours without recharging. The batteries are recharged by simply placing the complete transmitter in the automatic battery charging system located on the desk-model receiver. Recharging usually takes about three times the operating time. This is a convenient arrangement since the system is normally operated during daytime hours and automatically recharges overnight.

The Radio Receiver: The desk model radio receiver measures approximately 12 by 14 inches and is 8 inches high. A collapsible antenna extends to a height of about 3 feet. The receiver console contains the following controls and accessories: (1) *Channel selector switch* channels the electrocardiographic signal to (a) any conventional electrocardiographic recording instrument; (b) a cathode-ray oscilloscope; (c) a magnetic tape recorder and playback system (optional); or (d) multichannel operation permitting simultaneous recording on an electrocardiograph, continuous viewing on an oscilloscope, and recording on magnetic tape. (2) *Skin resistance meter* permits a fast and accurate measurement of the total body resistance between the electrodes as a check on proper electrode application. The plug on the cable is merely inserted into the resistance check jack on the console and the value of resistance read from the meter face. (3) *One millivolt calibration* is provided from the receiver console. This introduces a sharp square wave of one millivolt amplitude on the recording and oscilloscope instruments. Because of the high stability of the transmitter, there is almost no need for checking or resetting the calibration.

Summary of Method of Operation: The radioelectrocardiograph can broadcast the electrocardiogram over a distance of several hundred feet. Depending

* The pocket transmitter operates on an authorized radio frequency allocated by the Federal Communications Commission.

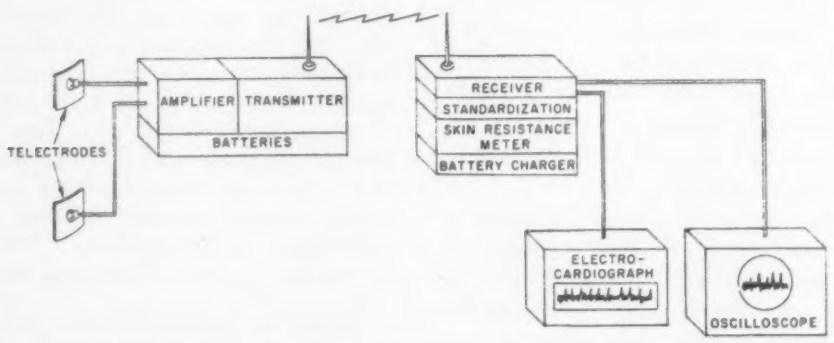


FIG. 2. Diagrammatic scheme of apparatus used in radioelectrocardiography. Impulse is transmitted from electrodes to the transmitter, where it is amplified and broadcast on a certain wave length to be picked up by the receiver. It is then fed to a conventional electrocardiograph or oscilloscope and may also be tape recorded.

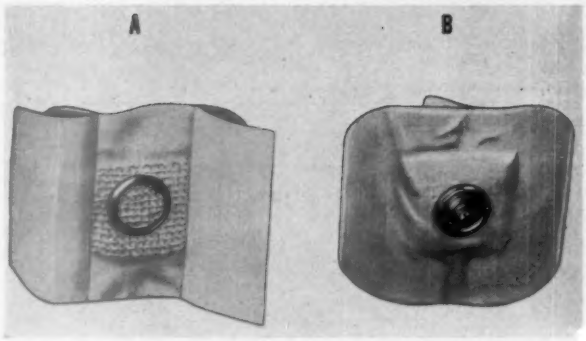


FIG. 3. Electrodes used in this study. "A" shows side which comes in contact with the skin. When not used, this side is protected by two folds of paper. The paste is applied within the metallic circle, which represents the inner part of the head of the snap shown in "B." "B" shows the external side of the electrode with the head of the snap on which the flexible wire is snapped. The electrodes are then covered and fixed to the skin with adhesive tape.

on the location of the equipment, building construction, height of the transmitter and situation of the receiver above ground level, and atmospheric conditions, the transmission range may extend from 200 to 1,200 feet. The electrical forces picked up by the electrodes are delivered by the connecting wires to the transmitter which is usually placed in the patient's pocket. The electrocardiogram obtained by the transmitter is broadcast on a radio-frequency beam and picked up by the receiver which may be situated close to or at a considerable distance from the patient. The information picked up by the receiver is then fed to a conventional electrocardiograph.

GENERAL PROCEDURE

The general procedure was as follows: a routine 12-lead electrocardiogram was taken with the patient in the recumbent position in the conventional manner. A control tracing was then taken in the recumbent and in the erect positions using the radioelectrocardiographic apparatus. The Master two-step test was next performed and the radioelectrocardiogram was recorded continually from the time of the control tracing, during the entire period of exercise, and about ten seconds immediately after discontinuing the exercise. (A pause of only one to two seconds was allowed between the end of the exercise tracing and that taken immediately after the exercise.) Tracings were also obtained in both the recumbent and upright positions, one, three, five and eight minutes after the exercise was discontinued. The tracing taken immediately after exercise by the technic used in these experiments has a somewhat different connotation than that used in the routine Master two-step test. Our tracings were actually recorded *immediately* after exercise for a period of two to eight seconds. Only one to two seconds intervened between the end of the exercise tracing and that taken

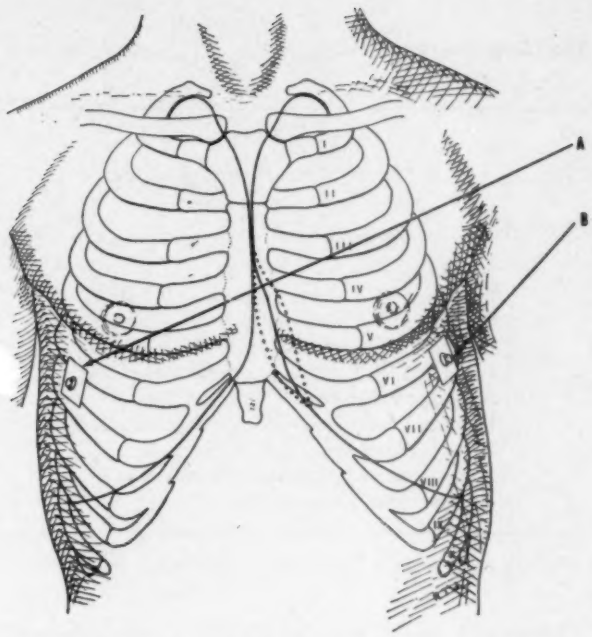


FIG. 4. Site of electrode placement usually employed in these studies. Electrode A is placed in the fifth interspace in the right mid-axillary line. Electrode B is placed in a similar position on the left side.

immediately after exercise. In the routine Master two-step test, the change from the upright to the recumbent position with the establishment of a steady readable baseline usually involves thirty seconds to one minute, so that the tracing taken immediately after exercise corresponds more to the tracing taken one minute after the cessation of the exercise.

CLINICAL MATERIAL

Three groups of patients were studied:

1. *Normal subjects.* This group included 127 persons (ninety-seven male, thirty female) eighteen to fifty-one years of age. All but five were below the age of forty years. Each person of this group was subjected to a double Master two-step test.

2. *Patients with myocardial abnormalities.* . This group consisted of 147 patients (sixty-nine male, seventy-eight female). The age of the patients ranged between twenty-four and seventy-six years; 134 patients were over the age of forty years. The disease was advanced to various stages, from benign uncomplicated essential hypertension to severe cardiovascular disease with heart failure. Thirty-eight patients had symptomatic coronary artery disease; six of these had had coronary occlusion.

3. *Patients with miscellaneous diseases.* This group consisted of twenty-two patients (seven male, fifteen female) suffering from diseases of the gastrointestinal tract (nine cases), thyroid dysfunction (four cases), chronic lung disease (three cases) and various other diseases (six cases). The ages ranged between twenty-one and sixty-eight years; ten patients were over the age of forty years.

TABLE I

Electrocardiographic Changes in 127 Normal Subjects during and after Exercise of a Double Master Two-Step Test

Electrocardiographic Changes	During Exercise		After Exercise	
	No. Cases	Per Cent	No. Cases	Per Cent
No changes	47	37	82	64
Decrease of T wave amplitude <1 mm.	15	12	15	12
Decrease of T wave amplitude >1 mm.	53	42	16	13
Increase in T wave amplitude >1 mm.	3	2	5	4
Inversion of T wave in occasional cycles	4	3	1	0.8
S-T depression of the junction type	17	13	15	12
Ischemic S-T depression in occasional cycles	5	4	1	0.8
Persistent ischemic S-T depression	1	0.8	1	0.8
Appearance of prominent U wave	1	0.8	0	0
Extrasystoles (3 or more)	0*	0	1	0.8

* One extrasystole appeared in two cases.

Groups 2 and 3 were subjected to the standard Master two-step test. The exercise was stopped if the patient manifested fatigue, precordial discomfort or shortness of breath.

Criteria Used in Determining the Type of Response: The following changes which were frequently observed in the normal group may be considered as a manifestation of a normal response: (1) the appearance or increase of a previously existing S-T segment depression of the junction type (jS-T); (2) lowering or increase of the amplitude of the T wave to complete flattening without actual inversion; (3) the disappearance of a previously existing U wave which is due to merging with the T wave during the tachycardia accompanying the exercise; (4) the appearance, as an isolated finding, of one of two premature beats during the period of exercise.

Because the electrocardiographic findings during exercise have not been well documented and since certain observations were obtained that differ from or are infrequently encountered in the postexercise electrocardiogram, a slight modification of the commonly accepted criteria of Master and others[9-15] was employed. The following findings were considered as evidence of abnormality: (1) the appearance of an ischemic S-T segment depression over 1 mm., or the increase over 1 mm. of a previously present S-T depression; (2) the appearance of S-T segment elevation over 1 mm., or the elevation of a previously depressed S-T segment; (3) T wave inversion; (4) the reversion of a previously negative T wave to an upright configuration; (5) frank U wave inversion; (6) the presence of numerous ectopic beats or their occurrence in pairs or coupling; and (7) marked changes in the configuration of the QRS complex (widening or narrowing of a previously widened QRS).

The following were considered to be suggestive of abnormality: (1) S-T depression observed in occasional beats; (2) T wave inversion observed in occasional beats; (3) the appearance of three or more premature beats during the period of exercise unaccompanied by any other findings; (4) the appearance of a prominent U wave; (5) marked alteration in T wave configuration.

RESULTS

1. *Normal Persons (127 Cases):* During exercise the heart rate increased by 30 to 90 per cent over the control resting value (average 43 per cent). Three minutes after discontinuing the exercise the heart rate was minus 26 to plus 15 per cent of the control values. The chief electrocardiographic change in this group consisted of varying degrees of decrease in amplitude of the T waves, leading often to complete flattening; this occurred in 54 per cent of the cases during exercise and in 25 per cent in the immediate postexercise period (Table I). Flattening of the T wave to the isoelectric line was usually observed in cases in which the T wave was of low voltage in the control resting electrocardiogram. S-T segment depression of the junction type occurred in 13 per cent of cases during exercise and in 12 per cent after exercise. As already mentioned, these changes when found in patients with cardiovascular disease were not considered as abnormal because of their frequent occurrence in the control group. This is also in accord with Master's criteria, according to which most of these changes are not considered to be abnormal.

Occasional cycles showing ischemic S-T segment depression or T wave inversion were found in 4 and 3 per cent of the cases, re-

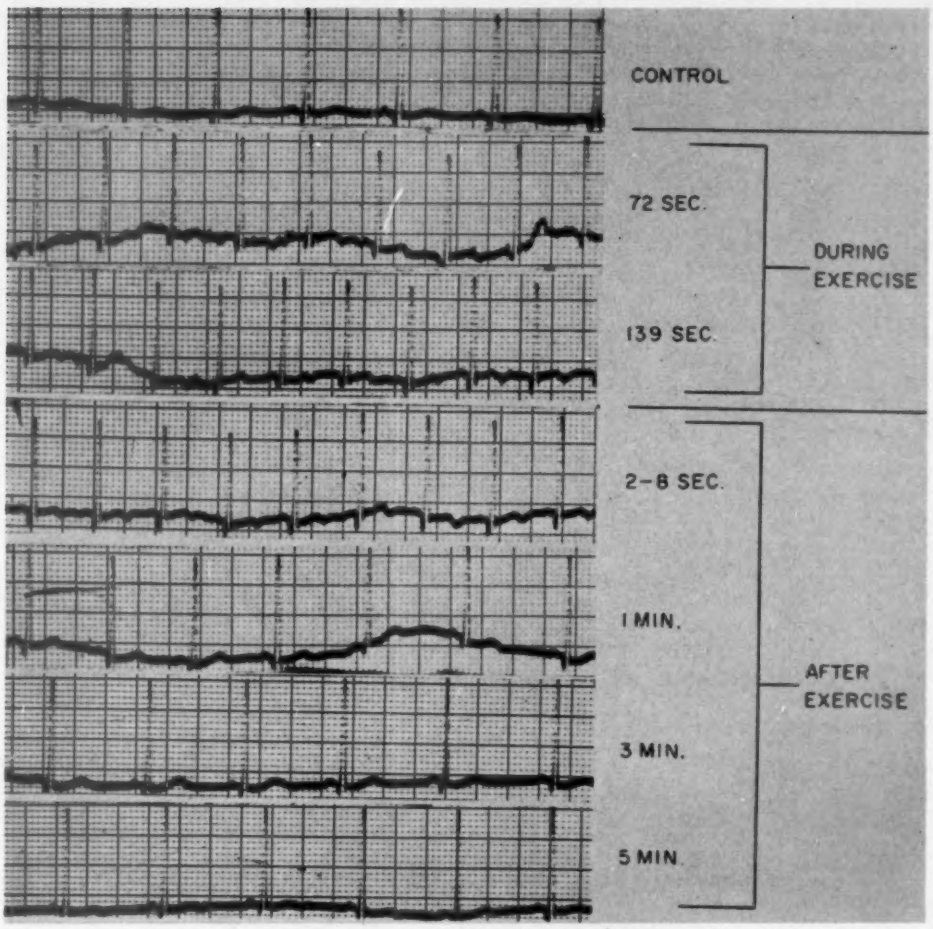


FIG. 5. *Probably abnormal response to a double Master two-step test* (42 trips in 3 minutes) in an apparently healthy, nineteen year old white man. Note that the control tracing shows low amplitude T waves. During exercise, there appears a tendency toward further flattening of the T wave followed by a terminal downward dip in some of the cycles. In the third strip, this becomes more pronounced, suggestive of an inverted T wave. This pattern persists in the tracing taken 2 to 8 seconds after exercise. Note that the T wave becomes upright in the strip taken 1 and 3 minutes after exercise and a slight suggestion of a terminal downward dip is seen in the tracing taken 5 minutes after the exercise. The most marked T wave changes are observed in the third strip taken after 139 seconds of exercise and in the tracing taken immediately after the exercise.

spectively, during exercise and in only one case after exercise. A prominent U wave appeared in only one case during exercise, and three extrasystoles appeared in another case following the exercise. In view of the infrequent occurrence of these changes in the control group, they were considered as probably abnormal changes when found in patients with cardiovascular disease. It should be noted that these changes appeared in the control group only after a double Master two-step test, while the patients with cardiovascular disease were subjected to a single Master two-step test.

One subject, an eighteen year old boy who was apparently healthy, manifested an ischemic S-T segment depression during the exercise, which persisted immediately after the exercise but disappeared one minute after discontinuing the exercise (Fig. 6).

It is of importance that all the aforementioned changes in the postexercise record were usually present only in the "immediate" postexercise record, i.e., two to eight seconds after discontinuing the exercise. Figures 5 and 6 illustrate some of the electrocardiographic changes infrequently observed in normal subjects.

2. *Patients with Hypertensive and/or Arteriosclerotic Cardiovascular Disease (147 Cases):*

A. *Patients with normal resting electrocardiograms (sixty-six cases).* During the exercise the heart rate increased by 18 to 120 per cent (average 46 per cent) above the control resting

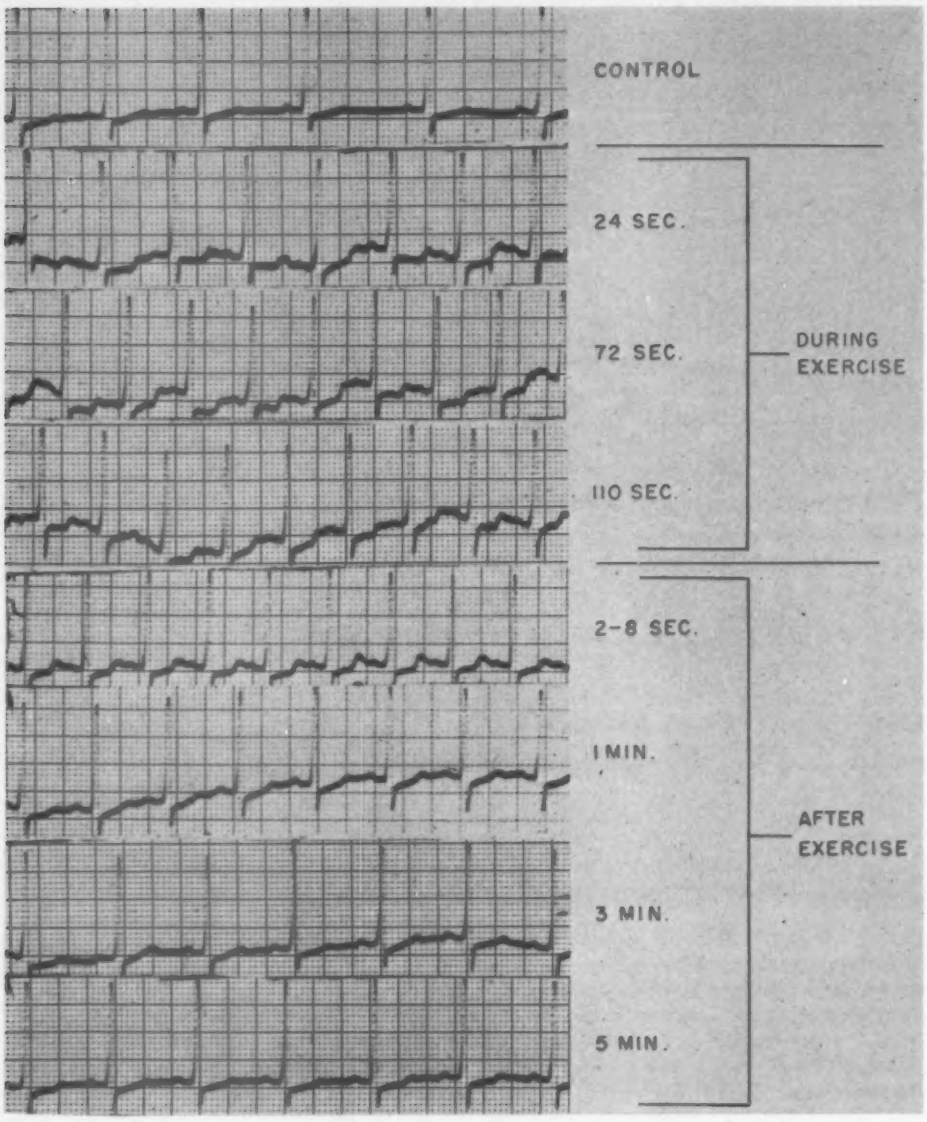


FIG. 6. *Abnormal response to a double Master two-step test* (36 trips in 3 minutes) in an apparently normal, eighteen year old white man. Note the low amplitude T waves and jS-T segment depression in the control tracing. Exercise was accompanied by the appearance of an ischemic type of S-T segment depression of up to 2 mm. This is also present in the tracing taken 2 to 8 seconds after the exercise and is absent 1, 3 and 5 minutes after the exercise. The maximal changes are observed in the tracings taken during and immediately after (2 to 8 seconds) the exercise period.

value; three minutes after the exercise was stopped it returned to minus 8 to plus 14 per cent of the resting value. It may be seen from Tables II and IV that, in this group of patients, abnormal electrocardiographic changes appeared in twenty-three cases during and/or after exercise (35 per cent). The changes were present *only during exercise* in seven patients (10.5 per cent), *only after exercise* in four patients (6 per cent), and *both during and after exercise* in twelve patients (18.5 per cent). In six cases of the last group the changes were much more pronounced during exercise than in the immediate postexercise period (Table IV). Therefore, in thirteen of the total sixty-six cases in this group (19.5 per cent), the electrocardiographic changes were limited to or were much more pronounced during the period of exercise, when compared with the postexercise period. In six of these thirteen cases the electrocardiogram was definitely abnormal during the period of exercise while in the remaining seven it was probably abnormal. In ten (62 per cent) of the sixteen patients who exhibited changes in the post-

TABLE II

Summary of Electrocardiographic Changes during and after Exercise in Sixty-Six Patients with Hypertensive and/or Arteriosclerotic Cardiovascular Disease with Normal Resting Electrocardiograms

Electrocardiographic Changes	No. Cases	Per Cent	S-T Depression	Occasional S-T Depression	T Wave Inversion	Occasional T Wave Inversion or Biphasic T	Multiple Extrasystoles	Prominent U Wave	Marked Changes in QRS
No change during and after exercise	43	66	...	...	...	...	...	....	...
Changes only during exercise	7	10.5	...	...	...	...	...	...	...
Abnormal	1		...	...	1	...	...	...	...
Probably abnormal	6		...	1	...	3	2	...	...
Changes only after exercise	4	6	...	...	...	...	...	...	...
Abnormal	2		2	...	1	...	1	...	...
Probably abnormal	2		...	...	...	...	...	2	...
Changes during and after exercise	12	18.5	...	...	...	...	...	...	...
Abnormal during	11		9	...	5	1	1	1	1
Probably abnormal during	1		...	1	...	...	...	...	...
Abnormal after	10		9	...	3	...	1	...	...
Probably abnormal after*	2		...	1	...	...	...	1	...

* In ten patients the changes were present *only* in the record taken *immediately* (two to eight seconds) after exercise.

exercise period, the changes were limited to the "immediate" postexercise period. Figure 7 demonstrates some of the typical alterations in these cases.

B. *Patients with abnormal resting electrocardiograms (eighty-one cases).* The abnormalities in the resting electrocardiograms of these patients consisted mainly of S-T segment and/or T wave changes in V_6 and other leads. The control tracing manifested various degrees of left ventricular strain, ischemic ST-T wave changes, infarct patterns, bundle branch block, and other types of abnormality. During the exercise the heart rate increased by 11 to 131 per cent over the control value (average 60 per cent) and returned to minus 6 to plus 28 per cent of the control, three minutes after discontinuing the exercise. It may be seen from Table III that no further changes appeared in 43 per cent of these cases. Twelve patients (15 per cent) of the total group showed abnormal changes *only during exercise*, one patient *only after exercise*, and thirty-three patients (41 per cent) *both during and after exercise*. Of the last group (thirty-three patients), fifteen patients showed more pronounced changes during the period of exercise when compared with those in the postexercise period (Table IV). Therefore, in twenty-seven of the total group of eighty-one patients (33 per cent) the electrocardiographic changes were either limited to or were much more pronounced during the period of exercise. In eleven (32 per cent) of the thirty-four patients who exhibited alterations in the postexercise period, the changes were limited to the "immediate" postexercise period (two to eight

TABLE III

Summary of Electrocardiographic Changes during and after Exercise in Eighty-One Patients with Hypertensive and/or Arteriosclerotic Cardiovascular Disease with ST-T Changes in the Control Resting Electrocardiogram

Electrocardiographic Changes	No. Cases	Per Cent	S-T Depression			S-T Elevation		T Wave			Tall U Wave	Marked Change in QRS	Multiple Extrasystoles
			Disappearance	Increase	Decrease	Appearance	Increase	Inversion	Reversion	Change in Contour			
No change during and after exercise	35	43	...	...	...	...	...	...	...	...	...	...	...
Change only during exercise	12	15	...	...	...	...	..	...	...	...	...	...	...
Abnormal	11		...	...	5	...	1	1	5	...	...	2	4
Probably abnormal	1	...	...	...	...	...	...	...	...	...	...	...	1
Change only after exercise	1	1	...	...	...	...	..	...	...	...	...	...	...
Abnormal	1		...	1	...	...	...	1	...	...	...	...	...
Changes during and after exercise	33	41	...	...	...	..	...	...	..	...	...	...	...
Abnormal during	32		5	14	7	1	...	7	10	...	3	1	7
Probably abnormal during	1		...	...	...	...	...	...	...	1	...	...	...
Abnormal after*	32		4	19	3	1	...	6	10	...	3	...	6
Probably abnormal after	1	...	...	...	...	...	...	...	...	1	...	...	...

* Eleven patients had changes *only* in the records taken *immediately* (two to eight seconds) after exercise.

TABLE IV

Comparison of Time of Appearance and Degree of Significant Electrocardiographic Changes in 147 Patients with Hypertensive and/or Arteriosclerotic Cardiovascular Disease

Electrocardiographic Changes	Normal Resting Electrocardiogram		Abnormal Resting Electrocardiogram		Total	
	No. Cases	Per Cent	No. Cases	Per Cent	No. Cases	Per Cent
Total number of cases	66	100	81	100	147	100
No change during and after exercise	43	65	35	43	78	53
Changes during and/or after exercise	23	35	46	57	69	47
Changes only during exercise	7	10.5	12	15	19	28*
Changes only after exercise	4	6	1	1	5	7*
Changes during and after exercise	12	18.5	33	41	45	65*
More during	6	9	15	18	21	30*
Equal during and after	4	6	11	13	15	22*
More after	2	3	7	10	9	13*
Changes Only or More during Exercise	13	19.5	27	33	41	58*

* Per cent of the sixty-nine cases in which changes occurred during and/or after exercise.

seconds after exercise). Figures 8 to 10 illustrate the changes in some of these cases.

3. *Patients with Symptomatic Coronary Artery Disease (Thirty-Eight Cases):* Thirty-eight of the 147 patients with hypertensive and/or arteriosclerotic cardiovascular disease had also symptomatic coronary artery disease. Six of these had had coronary occlusion. In fourteen of the thirty-eight patients the resting electrocardiogram was either completely normal or showed evidence of mild left ventricular hypertropy without ST-T changes. Electrocardiographic changes, suggesting probable abnormalities, appeared in two patients only during

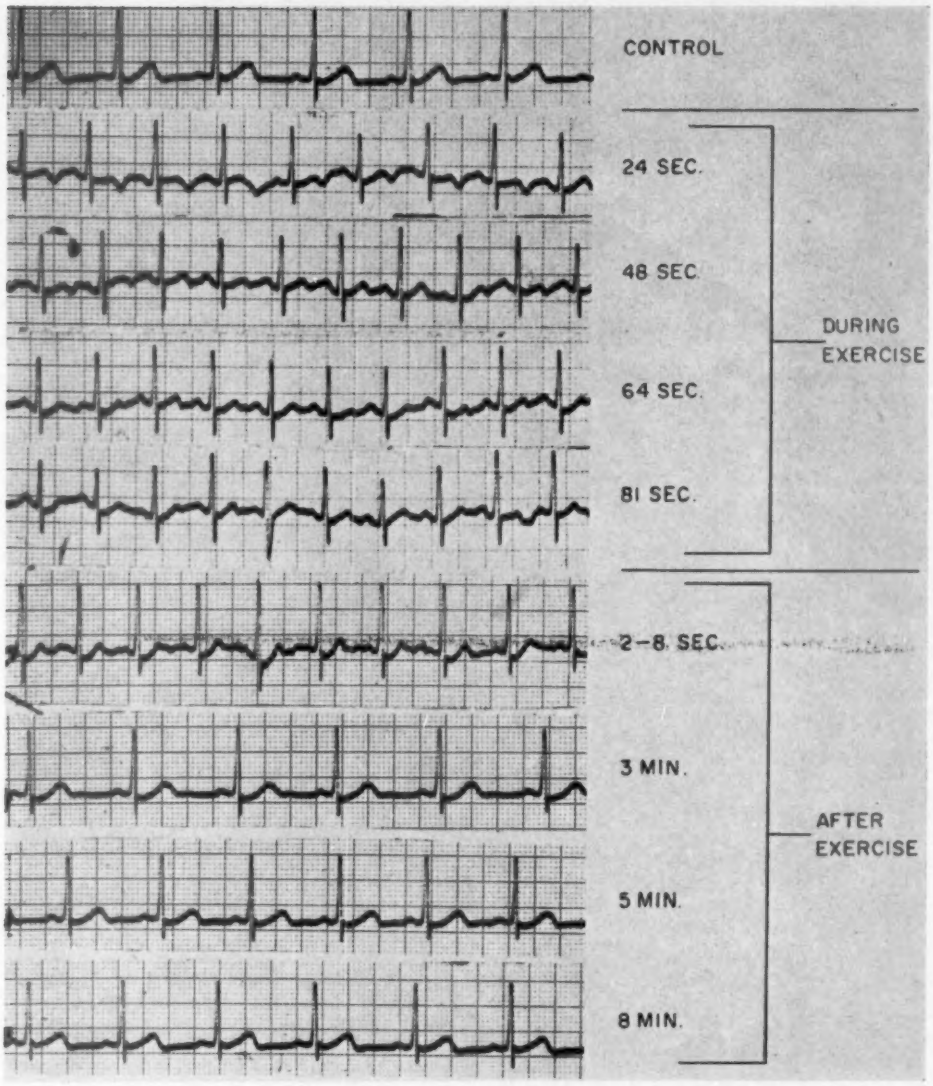


FIG. 7. *Abnormal response to a single Master two-step test* (19 trips in $1^1/_2$ minutes) in a thirty-eight year old Negro woman with benign essential hypertension. Note normal control tracing. The T waves became inverted during the first 24 seconds of exercise. This was much less marked at 48 seconds and was absent after 64 and 81 seconds. At this period ischemic S-T segment depression was observed in some cycles. The S-T segment depression persisted in the tracing taken 2 and 8 seconds following the exercise but returned to normal 3, 5 and 8 minutes after the exercise was discontinued.

the period of exercise. Three other patients showed a depression of the S-T segment both during and after exercise. In the group of twenty-four patients with abnormal resting electrocardiograms, four showed abnormal changes only during the period of exercise and six had changes both during and after the period of exercise. The changes consisted of an appearance or increase of the S-T segment depression, inversion of T waves, the appearance of runs of extrasystoles, and a marked S-T elevation (in one case). Here again the changes were usually more pronounced during the period of exercise and immediately after its discontinuance. In no case were changes observed only after the exercise was discontinued.* Figure 11 is an illustration of the changes in one patient from this group.

4. *Patients with Miscellaneous (Primarily Noncardiac) Diseases (Twenty-Two Cases):* Abnormal

* In comparing these results with those of others with coronary insufficiency it should be emphasized that only a single Master two-step test was employed in this series. In the reported data where a higher percentage of positive tests was obtained a double Master two-step test was usually employed.

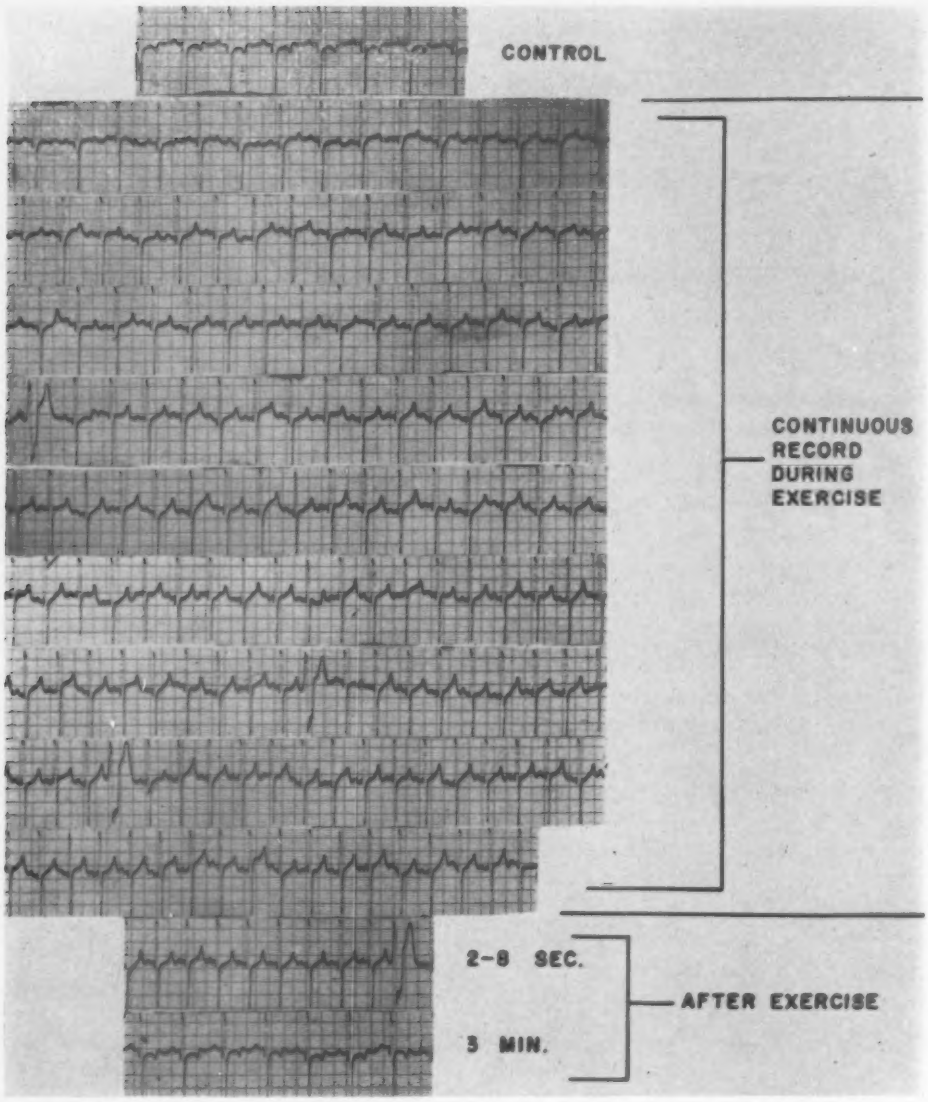


FIG. 8. *Abnormal response to a single Master two-step test* (21 trips in 1½ minutes) in a forty-eight year old Negro man with hypertensive and arteriosclerotic cardiovascular disease and congestive heart failure. Note ischemic S-T depression and inverted T waves in the control tracing. The continuous tracing during exercise shows the following features: (a) disappearance of S-T segment depression; (b) reversion of the T wave; and (c) appearance of ventricular premature beats. These findings developed gradually and persisted during the whole period of exercise and 8 seconds after its cessation. The tracings taken 3 and 5 minutes after exercise were similar to the control.

electrocardiographic changes appeared in seven cases during exercise and in three of this group after exercise (Table v). The abnormal findings occurred in patients with diseases which are likely to involve the heart, e.g., hyper- and hypothyroidism, severe anemia, etc.

Electrocardiographic Alterations in the Presence of Myocardial Abnormality; Comparison of the Changes during Exercise and in the Postexercise Period: The electrocardiographic changes observed during and following the period of exercise varied not only in degree but also in the type of alteration observed. The abnormal postexercise tracing showed changes similar to those reported in the Master two-step test and consisted of ischemic S-T segment depression, T wave inversion, and, occasionally, premature beats. However, exercise precipitated other alterations which are uncommon in the postexercise period. These include the following: decrease or disappearance of an S-T segment depression; reversion of a negative T wave to an upright configuration; appearance of a prominent U wave; and occasionally narrowing of a widened

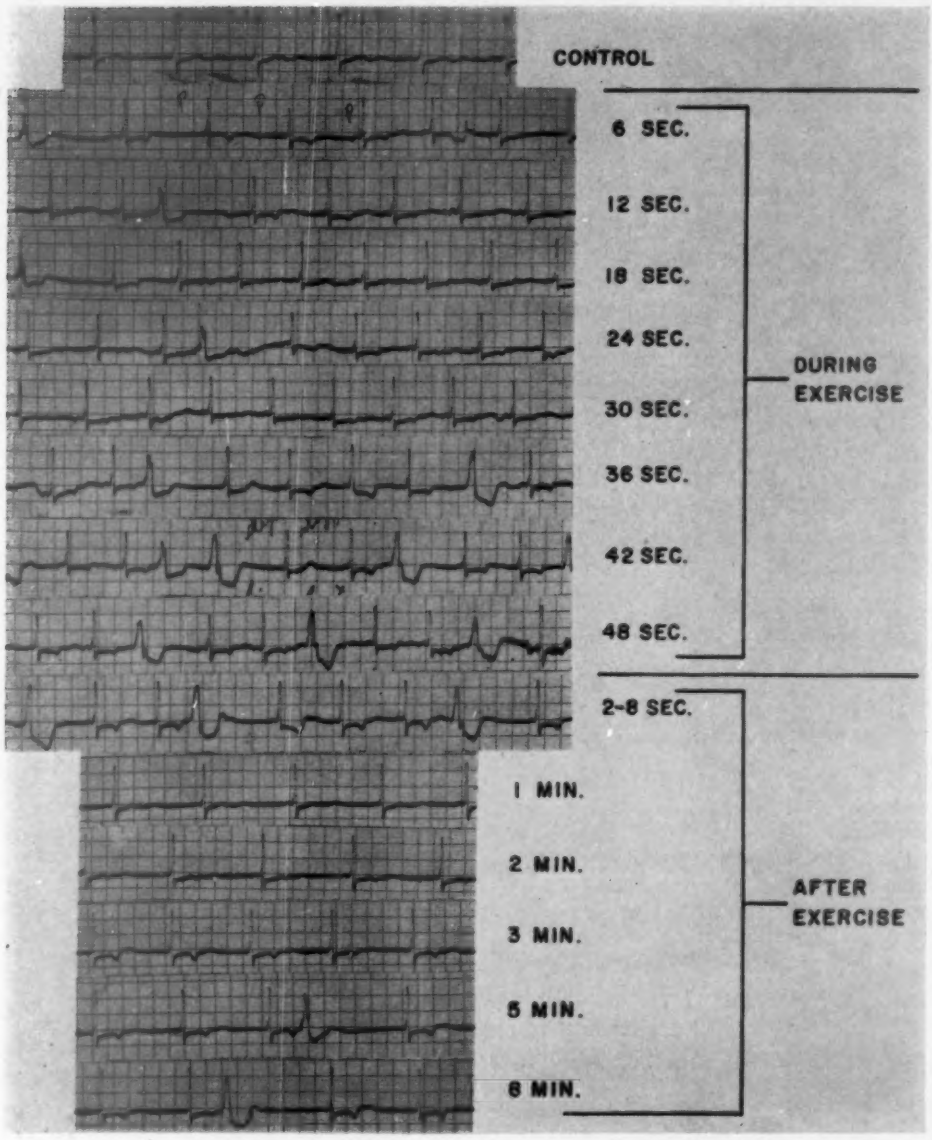


FIG. 9. *Abnormal response to a single Master two-step test* (16 trips in $1^1/_2$ minutes) in a seventy-five year old Negro woman with hypertensive and arteriosclerotic cardiovascular disease. Control tracing shows upright notched T waves of diminished amplitude. Note the appearance of inverted T waves, a wandering pacemaker (probably), and premature beats, 6 seconds after exercise. At 36 seconds the premature beats were more frequent, the inverted T waves persisted and there was, in addition, ischemic S-T segment depression. These changes became even more marked toward the end of the exercise period. At 1 minute after exercise, the tracing was similar to the control; at 2 minutes, there was a terminal downward dip of the T wave, and at 3, 5 and 8 minutes the T waves were again inverted and the S-T segment depressed. The illustration, therefore, shows the appearance of ischemic S-T segment depression, inverted T waves and premature beats during the exercise period, a return to the control tracing 1 minute after exercise and the reappearance of the abnormal findings in the tracings taken 3, 5 and 8 minutes after exercise.

QRS complex (three cases). Such changes were infrequently observed in the postexercise tracing except in the "immediate" (two to eight second) record as taken by radioelectrocardiography.

COMMENTS

Factors Producing Electrocardiographic Changes during Exercise: The electrocardiographic changes during exercise are not due to ischemia alone but probably to a combination of many factors. Inadequate supply of oxygen in the presence of increased demand is probably the main and decisive factor for the appearance of ischemic S-T segment depression and probably

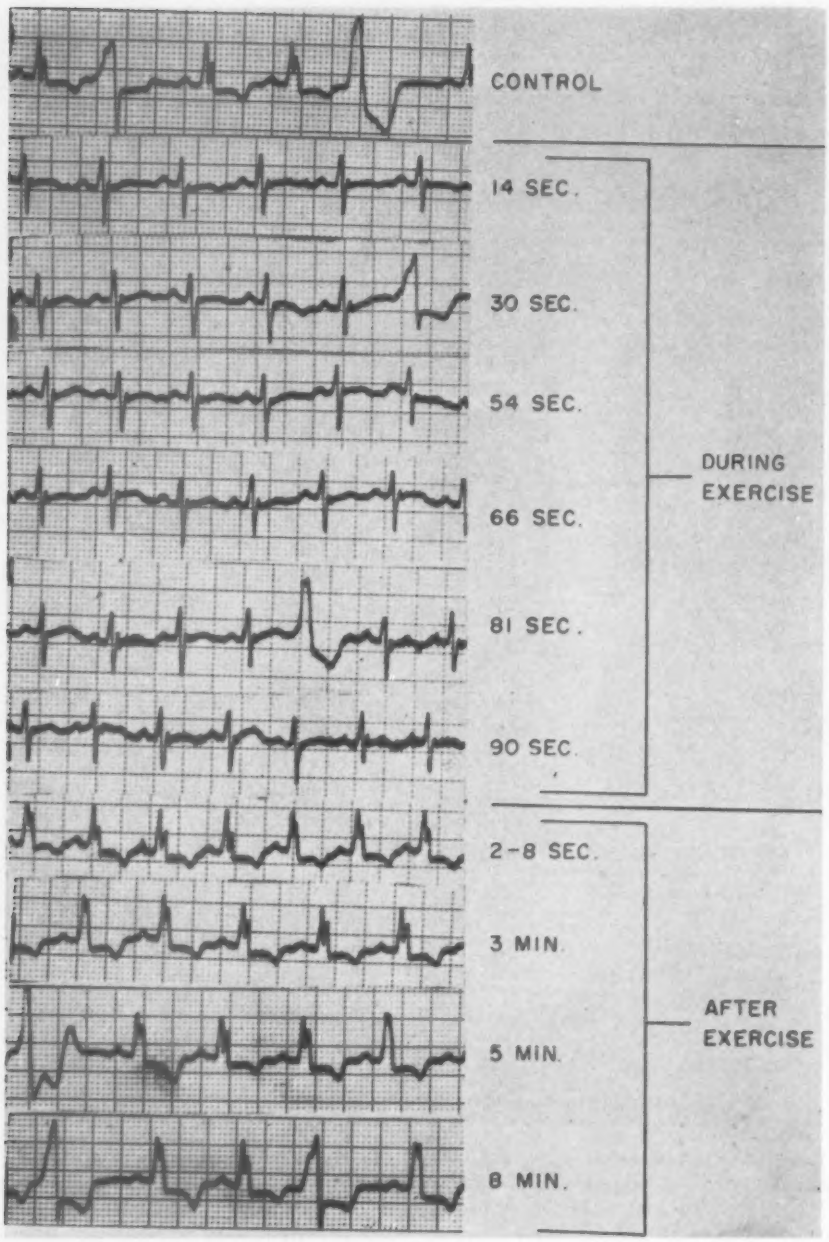


FIG. 10. *Abnormal response to a single Master two-step test* (17 trips in $1^1/_2$ minutes) in a fifty year old Negro man with hypertensive and arteriosclerotic cardiovascular disease and congestive heart failure. Note the presence of ventricular premature beats, wide and notched QRS complexes followed by inverted T waves in the control tracing (left bundle branch block). During the first 14 seconds of exercise, there was a narrowing of the QRS complexes, although this was not accompanied by a significant change in heart rate. The narrowed complexes were soon followed by upright T waves; this pattern persisted during the entire period of exercise. Note that immediately after exercise the tracing returned to the control pattern which persisted to the end of observation, at 8 minutes. The tracing during exercise appears therefore to be much closer to normal.

also of T wave inversion. However, the very frequently observed decreases in T wave amplitude without actual inversion of the T wave are probably related to autonomic nervous influences, vagal release and increased sympathetic tone. Hyperventilation and the accompanying fall in CO_2 content in the arterial blood may also be responsible for the non-

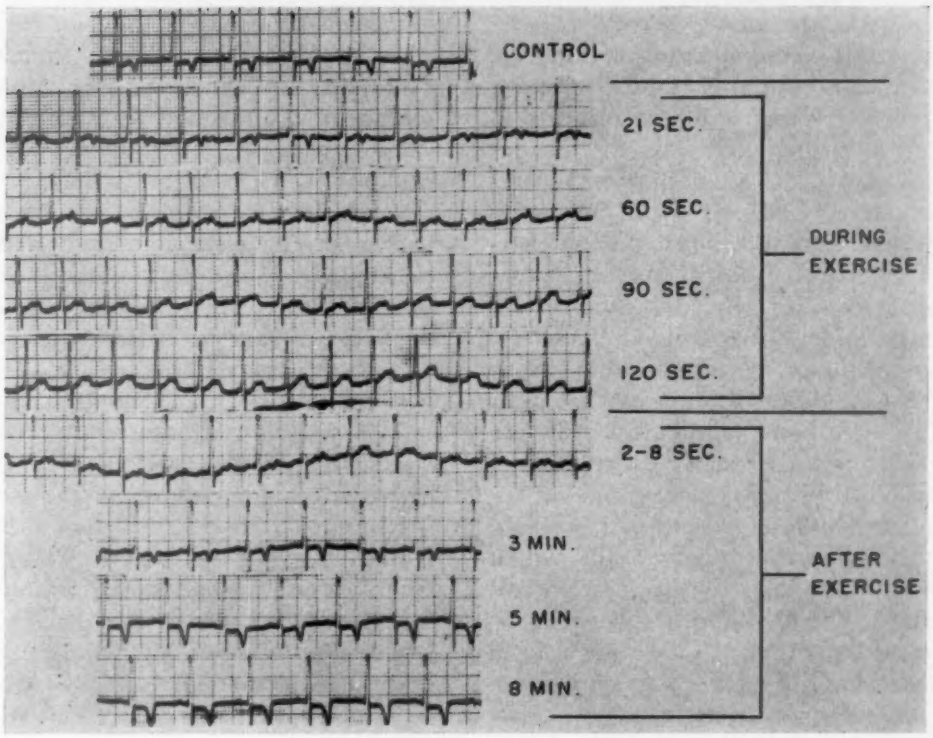


FIG. 11. *Abnormal response to a single Master two-step test* (23 trips in $1^1/_2$ minutes) in a 50 year old white man with angina pectoris. Note S-T depression and inverted T waves in the control tracing. During exercise the T wave became gradually upright. U waves appeared and gradually became more marked. In the last tracing taken during exercise (120 seconds), the U and T waves merged. In the tracing taken 2 to 8 seconds after exercise there was a tendency for the reappearance of an inverted T wave; the tracings taken 3, 5 and 8 minutes after exercise were similar to the control.

specific T wave changes and the appearance of a pronounced U wave. The increase in pulse rate *per se* may change the contour of the electrocardiogram and more particularly of the T and U waves by shortening the period of the diastole.

Cardiac Work during and in the Immediate Post-exercise Period; Relationship to the Electrocardiogram: Relatively few studies of continuous measurement of cardiac output, coronary blood flow, left ventricular work and efficiency are available.[19–23] Healthy unanesthetized dogs respond to a standard exercise (running on a treadmill at 3 m.p.h.) with an increase in pulse rate, aortic blood flow and left ventricular work.[24,25] The increase in cardiac output is not accompanied by a significant change in stroke volume, but is almost directly proportional to the heart rate.[24–26] Detailed studies on normal human subjects and in those with myocardial disease were performed by Donald et al.[27–31] These authors found that in healthy human subjects performing exercise equal to walking $1^1/_2$ to 5 m.p.h., the cardiac output rises to a peak within one minute, re-

TABLE V

Electrocardiographic Changes in Patients with Miscellaneous Diseases (Noncardiac) during and after Effort (Twenty-two Cases)

Electrocardiographic Changes	During Effort	After Effort
No change	15	18
S-T depression and/or T wave inversion	3	1
S-T elevation and/or T wave reversion	1	1
U wave appearance	3	1
Total abnormal	7	3
Only during exercise	4	
More changes during than after exercise	2	
More changes after than during exercise	1	

mains stable during the period of exercise, and returns to a steady resting state within one minute of discontinuing the exercise.[31] Reeves et al. have recently shown that the increase in cardiac output following exercise in the upright position was less marked than that in the recumbent position.[32] Coronary blood flow is increased in normal human subjects during exercise;[23] however, cardiac work increases more than the myocardial oxygen consumption, indicating an increase in left ventricular efficiency.

The response to exercise of patients with myocardial abnormalities varies somewhat from the normal group. For example, the response of patients with mitral stenosis differed from that of normal subjects in that many of the patients were incapable of raising their cardiac output to any important degree, and when they were, there was a delay in the achievement of the peak.[31–33] There was also a delay in the return of the cardiac output to the control level following cessation of exercise. A similar response was observed in hypertensive patients with exertional dyspnea and cardiac enlargement. In patients with myocardial disease, the work and the efficiency of the left ventricle fail to increase adequately in response to exercise.[23]

The aforementioned studies indicate that, as might be expected, the heart is under maximal strain during the first minute of exercise, when the metabolic demands are higher than normal, but the compensatory mechanisms are still not entirely operative. It is of interest that the electrocardiographic changes frequently appeared during the first minute of exercise, and disappeared thereafter, despite continued exercise. In patients with severe myocardial disease, the changes did not regress, but usually increased as exercise was continued, and sometimes were even more pronounced in the postexercise period. The latter phenomenon may be due to the decrease in pulse rate and the fall of cardiac output and coronary blood flow before the myocardium has recuperated from the increased metabolic demands of exercise.

Advantages of the Electrocardiogram during Exercise and of Radioelectrocardiography: The electrocardiogram taken during exercise has evident advantages over the postexercise electrocardiogram in the detection of coronary artery and myocardial disease. This is manifested by the fact that in 58 per cent of our subjects with cardiac disease who had abnormal responses, the changes were observed only or chiefly during exercise. This comparison is even more striking, because many of the postexercise changes were present only in the "immediate" postexercise record which was virtually a continuous record during the first ten seconds of the postexercise period. Many of these changes would probably have been missed in the "immediate" postexercise record in the Master two-step test with the conventional electrocardiograph, because this so-called "immediate" tracing is actually taken thirty to sixty seconds after the cessation of exercise. The occasional finding of more pronounced changes in the postexercise period indicates that the ideal diagnostic procedure would be a continuous recording both during the exercise period and one, three and five minutes after cessation of the exercise.

Although it is believed that the lead system employed (which corresponds to V_6) enabled us to secure valuable information that is obtainable from a single unipolar lead, the simultaneous use of other leads would probably give additional data. These will be employed with two- and three-channel receivers which are now being constructed. In addition to the electrocardiogram the simultaneous recording of respiration, blood pressure and electroencephalogram by multichannel apparatus would give us additional important data.

Radioelectrocardiography possesses many advantages over the conventional electrocardiograph in the study of the electrocardiogram during exercise. The records may be taken while the patient is situated at a distance from the recording apparatus, e.g., while the patient is at home or in another section of the hospital; they may be observed continuously by the physician while he is not in the patient's room, and they may be tape-recorded and replayed at a convenient time. Radioelectrocardiography makes possible the assessments of various types of work on the cardiovascular system, and may therefore be of value in industrial medicine.

Summary

The electrocardiogram during the standard Master two-step test was studied and compared with the postexercise tracings in a total of 296 subjects. A radioelectrocardiograph system based on the principle of broadcasting the electrocardiogram was used. The records obtained with this method show a steady baseline. In addition the method permits the taking of records during various forms of activity performed far from the recording apparatus.

The changes during exercise in 127 apparently

healthy persons below the age of forty years consisted of a decrease of the amplitude of the T wave to complete flattening (54 per cent), S-T segment depression of the junction type (13 per cent), occasional ischemic S-T segment depression (4 per cent) or T wave inversion (3 per cent) and occasional extrasystoles. Only one subject had persistent ischemic S-T segment depression.

The following criteria for abnormality were used: appearance or increase of an ischemic S-T segment depression over 1 mm.; elevation of an isoelectric or previously depressed S-T segment over 1 mm. of the control; T wave inversion; reversion of a negative T wave to an upright position; marked changes in the contour of the QRS complex; or appearance of multiple extrasystoles.

Sixty-six patients with hypertensive and/or arteriosclerotic cardiovascular disease with normal resting electrocardiograms or evidence of mild left ventricular hypertrophy showed the following electrocardiographic changes during and after exercise: 19.5 per cent had probably or definitely abnormal records only or chiefly during exercise; 9 per cent had changes only or chiefly after exercise; and 6 per cent had equal changes during and after exercise.

Eighty-one patients with hypertensive and/or arteriosclerotic cardiovascular disease with abnormal resting electrocardiograms (ST-T changes in one or more leads) showed the following changes during and after exercise: 33 per cent had abnormalities only or chiefly during exercise; 11 per cent only or chiefly after exercise; and 13 per cent both during and after exercise.

Of thirty-eight patients with symptomatic coronary artery disease (included in the 147 patients with hypertensive-arteriosclerotic cardiovascular disease), six had changes only or chiefly during exercise and nine both during and after exercise.

Of twenty-two patients with miscellaneous (primarily noncardiac) diseases, seven had abnormalities during exercise and only three after exercise.

It is concluded that the electrocardiogram during exercise is an extremely valuable adjunct in the detection of myocardial disease since the information obtained during this period is often unavailable or inadequately shown in the postexercise period.

Acknowledgment

We wish to express our appreciation to Mr. Richard M. Berman and Mr. Bernard Schwartz for their technical assistance.

References

1. Dunn, F. L. and Rahm, W. E., Jr. Electrocardiography: modern trends in instrumentation and visual and direct recording electrocardiography. *Ann. Int. Med.*, 32: 611, 1950.
2. Beenken, H. G. and Dunn, F. L. Short distance radio telemetering of physiological information. *I.R.E. Tr. M. Electronics*, PGME-12, p. 53, 1958.
3. Dunn, F. L. and Beenken, H. G. Short distance radio telemetering of physiological information. *J. A. M. A.*, 169: 1618, 1960.
4. Holter, N. J. and Gengerelli, J. A. Remote recording of physiological data by radio. *Rocky Mountain M. J.*, 46: 749, 1949.
5. Holter, N. J. Radioelectrocardiography: a new technique for cardiovascular studies. *Ann. New York Acad. Sc.*, 65: 913, 1957.
6. MacInnis, H. F. The clinical application of radioelectrocardiography. *Canad. M. A. J.*, 70: 574, 1954.
7. Carbery, W. J., Tolles, W. E. and Freiman, A. H. A system for monitoring the ECG under dynamic conditions. *Aerospace Med.*, 31: 131, 1960.
8. Freiman, A. H., Tolles, W., Carbery, W. J., Ruegsegger, P., Abarquez, R. F. and LaDue, J. S. The electrocardiogram during exercise. *Am. J. Cardiol.*, 5: 506, 1960.
9. Master, A. M. Electrocardiogram and "two-step" exercise: test of cardiac function and coronary insufficiency. *Am. J. M. Sc.*, 207: 435, 1944.
10. Master, A. M., Field, L. E. and Donoso, E. Coronary artery disease and "two-step" exercise test. *New York J. Med.*, 57: 1051, 1957.
11. Master, A. M., Rosenfeld, I. and Donoso, E. The Master "2-step" exercise test. *Advances Cardiol.*, 2: 243, 1959.
12. Thomas, C. B. The cardiovascular response of normal young adults to exercise as determined by the double Master two-step test. *Bull. Johns Hopkins Hosp.*, 89: 181, 1951.
13. Robb, G. P., Marks, H. H. and Mattingly, T. W. The value of the double standard two-step exercise test in the detection of coronary disease: A clinical and statistical follow-up study of military personnel and insurance applicants. *A. Life Insurance M. Directors America*, 40: 52, 1957.
14. Russek, H. I. Master two-step test in coronary artery disease. *J. A. M. A.*, 165: 1772, 1957.
15. Lepeschkin, E. and Surawicz, B. Characteristics of true-positive and false-positive results of electrocardiographic Master two-step exercise tests. *New England J. Med.*, 258: 511, 1958.
16. Brody, A. J. Master two-step test in clinically unselected patients. *J. A. M. A.*, 171: 1195, 1959.
17. Lepeschkin, E. Exercise tests in the diagnosis of coronary heart disease. *Circulation*, 22: 986, 1960.
18. Scherf, D. Development of the electrocardiographic exercise test. Standardized versus nonstandardized test. *Am. J. Cardiol.*, 5: 433, 1960.
19. Bishop, J. M., Donald, K. W. and Wade, O. L. Circulatory dynamics at rest and on exercise in hyperkinetic states. *Clin. Sc*, 14: 329, 1955.
20. Taylor, S. H., Donald, K. W. and Bishop, J. M. Circulatory studies in hypertensive patients at rest and during exercise, with a note on the Starling relationship in the left ventricle in essential hypertension. *Clin. Sc.*, 16: 351, 1957.

21. Barger, A. C., Richards, V., Metcalfe, J. and Günther, B. Regulation of the circulation during exercise: cardiac output (direct Fick) and metabolic adjustments in the normal dog. *Am. J. Physiol.*, 184: 613, 1956.
22. Wyndham, C. H. and Ward, J. S. An assessment of the exercise capacity of cardiac patients. *Circulation*, 16: 384, 1957.
23. Lombardo, T. A., Rose, L., Taeschler, M., Tully, S. and Bing, R. J. The effect of exercise on coronary blood flow, myocardial oxygen consumption and cardiac efficiency in man. *Circulation*, 7: 71, 1953.
24. Rushmer, R. F. Cardiovascular Dynamics, 2nd ed. Philadelphia, 1961. W. B. Saunders Co.
25. Rushmer, R. F., Smith, O. A., Jr. and Franklin, D. L. Mechanisms of cardiac control during exercise. *Circulation Res.*, 7: 602, 1959.
26. Wang, Y., Marshall, R. J. and Shepherd, J. T. Stroke volume in the dog during graded exercise. *Circulation Res.*, 8: 558, 1960.
27. Donald, K. W., Bishop, J. M. and Wade, O. L. Study of minute to minute changes of arteriovenous oxygen content difference, oxygen uptake and cardiac output and rate of achievement of steady state during exercise in rheumatic heart disease. *J. Clin. Invest.*, 33: 1146, 1954.
28. Donald, K. W., Bishop, J. M., Cumming, G. and Wade, O. L. Effect of exercise on cardiac output and circulatory dynamics of normal subjects. *Clin. Sc.*, 14: 37, 1955.
29. Donald, K. W., Bishop, J. M. and Wade, O. L. Changes in oxygen content of axillary venous blood during leg exercise in patients with rheumatic heart disease. *Clin. Sc.*, 14: 531, 1955.
30. Donald, K. W. Exercise studies in heart disease. *Mod. Concepts Cardiovas. Dis.*, 28: 6, 1959.
31. Donald, K. W. Exercise and heart disease. *Brit. M. J.*, 1: 985, 1959.
32. Reeves, J. T., Grover, R. F., Blount, S. G., Jr. and Filley, G F. Cardiac output response to standing and treadmill walking. *J. Appl. Physiol.*, 14: 283, 1961.
33. Draper, A., Heimbecker, R., Daly, R., Carroll, D., Mudd, G., Wells, R., Falholt, W., Andrus, E. C. and Bing, R. J. Physiologic studies in mitral valvular disease. *Circulation*, 3: 531, 1951.

Review

Physiologic Regulation of Arterial Pressure*

ARTHUR C. GUYTON, M.D.

Jackson, Mississippi

WHEN SPEAKING of regulation of arterial pressure, different persons think of different types of regulation. For instance, the renal physiologist immediately thinks of regulation of pressure by the kidneys over a period of weeks, months or years. On the other hand, the neurophysiologist thinks of rapid reflex adjustments that regulate arterial pressure over a period of seconds or minutes, these reflexes opposing changes in pressure that result from alteration of body position, rapid loss of blood, etc. However, these two types of regulation are only parts of the complex system that regulates arterial pressure, for at least three other major mechanisms of regulation of arterial pressure are also known to occur, as will be discussed at greater length in this paper.

Regulation of arterial pressure subserves two main purposes, one of which is to oppose transient changes in pressure and the other to set the long term base level at which the arterial pressure is maintained. Therefore, this paper will be divided into two separate divisions: first, a description of the mechanisms that oppose rapid or relatively rapid alterations in pressure and second, a description of the basic long-term regulation of mean arterial pressure.

SYSTEMS THAT OPPOSE RAPID OR RELATIVELY RAPID CHANGES IN ARTERIAL PRESSURE

1. The Pressoreceptor Reflex System: The best known of the systems that oppose rapid changes in arterial pressure is the pressoreceptor reflex system, which is also called the "moderator system," the "buffer nerve system," the "baroreceptor system" or the "carotid sinus reflex system." If the arterial pressure increases, the walls of the systemic arteries become stretched, which stimulates the "pressoreceptors" located in the walls of (1) the internal carotid arteries immediately above the bifurcations of the common carotids, (2) the arch of the aorta and (3) isolated portions of the innominate and subclavian arteries. A barrage of impulses flows to the medullary portion of the brain where they inhibit the sympathetic nervous system and excite the parasympathetics. Inhibition of the sympathetics decreases the activity of the heart and also causes dilatation of the peripheral arterioles. At the same time, excitation of the parasympathetics to the heart through the vagi further depresses cardiac activity. The net result is reduced arterial pressure.

To summarize the pressoreceptor reflex, an initial increase in arterial pressure causes a feedback response that in turn reduces arterial pressure. Conversely, if the arterial pressure falls, the number of impulses transmitted from the pressoreceptors becomes reduced, and opposite effects occur throughout the circulatory system, the heart becoming a stronger pump and the peripheral vessels becoming constricted, thereby elevating the pressure.

We need now to analyze *the importance of the pressoreceptor system* in the regulation of arterial pressure. First, we must note that many different research workers have demonstrated the pressoreceptor system to be a short-term instead of a long-term regulator of arterial pressure.[1] The evidence for this is the following: If the arterial pressure remains elevated for several weeks because of some circulatory abnormality, the pressoreceptor system gradually adapts itself to this new pressure level and thereafter will oppose a change of pressure from the new

* From the Department of Physiology and Biophysics, University of Mississippi School of Medicine, Jackson, Mississippi. The original work quoted in this paper was supported by a Research Grant-in-Aid from the National Institutes of Health, U. S. Public Health Service.

level. That is, if disease of the kidneys has caused the mean arterial pressure to rise from a normal value of 100 up to 150 mm. Hg, a sudden fall in pressure from 150 will elicit pressoreceptor reflexes that will oppose the decrease. Thus, the baseline of operation of the pressoreceptor reflex system has been set at a higher level. This is analogous to setting the thermostat in one's house to a different level. Because adaptation of the pressoreceptor system comes about over a period of several weeks, pressoreceptor reflexes almost certainly are not of importance in regulating arterial pressure month after month or year after year, despite the protestations of a few research workers, most notable among whom is Heymans.[2]

On the other hand, the pressoreceptor system is extremely important in preventing rapid rises or declines in arterial pressure resulting from sudden changes in body position, sudden changes in blood volume, acute myocardial infarction or other acute circulatory stresses.

The pressoreceptor system acts almost instantly, the first evidences of the reflexes appearing in approximately three to four seconds.[3] Within approximately twenty-five to thirty seconds the reflex will have become maximally active. Because of this rapidity of action, the pressoreceptor system is by far the most important of all the arterial pressure regulatory mechanisms for keeping the arterial pressure from rising or falling excessively from second to second or moment to moment.

We need also to give some idea of *the value of the pressoreceptor system from a quantitative point of view*. Unfortunately, the quantitative importance of the pressoreceptor system in regulating arterial pressure is not known for the human being. However, in the dog a sudden increase in arterial pressure caused by sudden increase in blood volume is immediately two-thirds compensated by the pressoreceptor reflex mechanism; that is, the arterial pressure falls two-thirds the way back toward normal.[4] There is much reason to believe that the human being, who represents an upright animal, has an even more effective pressoreceptor system than that of the dog.[5] We might estimate, therefore, that the pressoreceptor system of the human being can compensate in the order of 80 per cent for intermittent changes in pressure that would otherwise result from various extraneous conditions.

As an example of pressoreceptor reflex function in the human being, a totally sympathectomized person has no significant pressoreceptor reflex system because he has lost the major portion of the efferent limb of this reflex. When he stands up suddenly, he is very likely to faint, simply because of lack of the immediate compensation that the pressoreceptor system normally affords.

2. The Central Nervous System Ischemic Response: Another very important circulatory reflex mechanism that helps to regulate arterial pressure under special conditions is the central nervous system ischemic response. This reflex is actually far more powerful than the pressoreceptor reflex, but it is activated only under special conditions. *Normally, a fall in arterial pressure down to as low as 50 mm. Hg will not elicit the central nervous system ischemic response, but a further fall from 50 down to approximately 20 mm. Hg causes the vasomotor center to become maximally excited.* Measurements in our laboratory indicate that the sympathetic nervous system is excited some four to six times as greatly by this response as by the pressoreceptor mechanism.[6] Obviously, such extreme sympathetic stimulation will excite the heart and constrict the peripheral blood vessels, thus tending to prevent further decrease in arterial pressure.

What is the value of the central nervous system ischemic response in acute regulation of arterial pressure? Obviously it has particular value when the arterial pressure approaches lethal levels. Indeed, the pressure range in which the ischemic response becomes activated is approximately the lowest pressure at which a person can survive for as much as one to three hours. Therefore, this pressure regulatory mechanism can be considered to be a "last ditch stand," powerfully activating the sympathetic nervous system and thereby keeping the arterial pressure from falling the additional amount that would be lethal. Undoubtedly, the lives of literally millions of persons suffering from severe shock have been saved by this extremely powerful central nervous system ischemic response.

Another instance in which the central nervous system ischemic response is very important is when the cerebrospinal fluid pressure rises very high or when a tumor of the brain compresses the vasomotor center. In either instance, the vessels supplying the vasomotor center can become so compressed that the vasomotor center becomes ischemic. This ischemia in turn elicits the ischemic response, causing sympathetic discharge throughout the body to elevate the arterial pressure. The increased

pressure inside the cerebral vessels then opens them up again and thereby maintains the life of the patient. Indeed, if the cerebrospinal fluid pressure continues to rise, this response becomes progressively more and more active, always keeping the arterial pressure slightly above that value which will provide adequate nutrition to the brain—that is, until the limit is finally reached beyond which the heart simply cannot pump.

3. The "Stress Relaxation" Mechanism of Arterial Pressure Regulation: Another mechanism for preventing rapid changes in arterial pressure, about which very little is known and which has had almost no publicity, is the so-called stress relaxation mechanism. That is, if the blood volume increases greatly, thereby causing arterial pressure to rise to excessive heights, the blood vessels of the circulatory system simply stretch over a period of a few minutes until they can accommodate the increased quantity of blood without excessive elevation of the pressure.[7] It is mainly the veins that thus increase their volume. Conversely, if a person loses a large volume of blood, the blood vessels—again especially the veins—immediately begin to contract around the remaining blood. After a few minutes time the force exerted by the vascular walls against the blood has returned almost to normal. As a result, even with reduced blood volume, the cardiac output and arterial pressure often rise almost back to normal.

To analyze the importance of the stress relaxation mechanism in regulation of arterial pressure, we must first consider how much is known about the mechanism. Studies particularly by Alexander,[7] Remington,[8] and others have demonstrated that stress relaxation occurs to a major extent in almost all smooth muscle tissues. This is particularly true of the smooth muscle in the venous walls. In other words, smooth muscle adapts its length automatically to approximately that required of it. If the blood volume is very great, the veins automatically adapt themselves to accommodate the excess blood volume. Conversely, if the blood volume is considerably reduced, the veins automatically accommodate their sizes to smaller values. Furthermore, one must note that the stress relaxation mechanism is still as effective as ever even when all reflex mechanisms have been completely blocked by administration of total spinal anesthesia or by any other procedure. For instance, in an animal whose circulatory reflexes have been completely blocked, rapid bleeding of 15 per cent of the blood volume will usually be almost lethal because the circulatory reflexes are not present to protect the arterial pressure. However, if the animal survives the acute bleeding, gradually over a period of thirty minutes to an hour the arterial pressure rises back to essentially normal values even in the absence of circulatory reflexes.[9] At least a major share of this return of arterial pressure to normal limits seems to result from the stress relaxation mechanism. The pressure returns approximately half way to normal every ten minutes; that is, if the pressure has been depressed initially to 40 mm. Hg, it will return to approximately 70 in ten minutes, to approximately 85 in twenty minutes, to 93 mm. Hg in thirty minutes, etc. This, obviously, is a much more slowly reacting mechanism than the five to thirty-second pressoreceptor reflex mechanism but, nevertheless, once it has reacted it is probably even more powerful than the pressoreceptor mechanism in affecting the circulation.

4. The "Capillary Fluid Shift" Mechanism for Arterial Pressure Regulation: Still a fourth important mechanism, the capillary fluid shift mechanism, also helps to moderate changes in arterial pressure, particularly when the blood volume becomes either too little or too great. It may be described as follows:

If a very large transfusion is given rapidly to an animal—in a matter of a few seconds—the arterial pressure will rise sometimes to as much as twice normal values, but then, during the ensuing ten minutes to an hour, the arterial pressure will gradually return to normal. Part of this return is caused by the reflex and stress relaxation mechanisms discussed previously, but, also, a major share of the return is caused by loss of fluid out of the circulation into the interstitial spaces.[10] Indeed, if the circulation has been greatly overloaded with blood, the pores in some capillary beds seem to become greatly stretched,[11] thus leading to even more rapid loss of fluid and protein from the circulation. Therefore, this is a very important mechanism for the regulation of arterial pressure.

Conversely, when a person is bled severely, the capillary fluid shift mechanism helps to bring the blood volume back to normal values and thereby aids in the return of arterial pressure to normal. The mechanism works in the following manner: A decrease in blood volume results not only in decreased arterial pressure but also in decreased capillary pressure. Yet, the

plasma in the capillaries still has a high colloid osmotic pressure resulting from the plasma proteins. The colloid osmotic pressure, being unopposed by normal capillary pressure, now causes osmosis of fluid from the extracapillary spaces into the circulation. The fluid in turn increases the plasma volume and gradually returns the circulating blood volume to normal limits; this obviously causes the arterial pressure also to return to essentially normal values. Thus, this mechanism constitutes both an important blood volume regulatory mechanism and an important regulatory mechanism of arterial pressure.

Recovery from diminished blood volume as a result of the capillary fluid shift mechanism does not occur nearly so rapidly as one might expect. For instance, in animals bled very severely, there may be very little increase in blood volume for as long as twenty-four hours if the animal had been slightly dehydrated prior to the bleeding.[12] On the other hand, if the animal had been drinking reasonable amounts of water and had had a considerable amount of fluids in the gastrointestinal tract at the time of the bleeding, then his blood volume may recover considerably during the first few hours. Thus, it appears that the capillary fluid shift mechanism can transfer fluid easily from the gastrointestinal tract but not to a great extent from most other parts of the body, unless there is an extra amount of fluid stored in these tissues before bleeding.

It is the gastrointestinal tract that is the source of most of the fluid to replenish blood volume; therefore, we also need to consider two alimentary mechanisms having to do secondarily with regulation of arterial pressure. These are the *thirst mechanism* and the *appetite for salt*. When the arterial pressure falls so low that semishock develops, the person almost invariably has an extreme thirst[13] as well as at least some increased appetite for salt. Because water and salt constitute the principal ingredients necessary to return the blood to normal volume, and because the thirst and appetite mechanisms cause the person to ingest water and salt, one can readily see that these mechanisms, too, constitute very important arterial pressure regulatory mechanisms that can actually save the life of the patient under certain conditions.

Long-Term Regulation of Mean Arterial Pressure

In discussing these mechanisms for arterial pressure regulation, we have noted that they act rapidly—in a matter of seconds in the case of the reflex mechanisms and in a matter of minutes or hours in the case of the stress relaxation and capillary fluid shift mechanisms. However, none of them has been proved to be of particular significance in regulating the mean level of arterial pressure over a period of weeks or months or years. Instead, such long-term regulation of arterial pressure seems to be vested entirely in the kidneys and associated nervous and hormonal mechanisms. There are at least three known ways in which the kidneys enter into the regulation of the arterial pressure; these are: (1) local hemodynamic responses of the kidneys themselves to changes in arterial pressure; (2) response of the kidneys to nervous reflexes that in turn are initiated by changes in arterial pressure; and (3) response of the kidneys to hormones secreted in response to changes in arterial pressure.

1. Hemodynamic Response of the Kidneys to Changes in Arterial Pressure: At reduced arterial pressures, the renal outflow of fluid and salts from the circulation—that is, the urinary output—becomes greatly reduced, whereas at elevated arterial pressures the outflow of fluid and salts becomes greatly increased.[14] Consequently, the blood volume becomes enhanced whenever the arterial pressure falls and the enhanced volume in turn helps to correct the reduced arterial pressure. Conversely, the blood volume decreases when the arterial pressure rises too high, this also acting as a feedback mechanism to reduce the arterial pressure toward normal limits.

The importance of this renal hemodynamic mechanism for regulating arterial pressure has often been questioned. However, in at least one instance we know it to be one of the most important of all the regulatory mechanisms of arterial pressure, and this occurs following very severe hemorrhage. When the arterial pressure falls below approximately 60 mm. Hg, there is essentially no output of urine. Therefore, all fluids and salts in the circulation and extracellular fluids are conserved. Then, as fluids can be built up by the capillary fluid shift mechanism, the blood volume returns to normal limits rather than the fluids continuing to be lost through the kidneys. This oligemic state of the kidneys, therefore, is actually one of the life-saving arterial pressure regulatory mechanisms.

On the other hand, the significance of this

mechanism in reducing arterial pressure when it rises too high is still somewhat doubtful. Yet, in several hundred experiments performed by Langston in our laboratory[14] during the past few years, we have always observed increase in fluid and salt output through the kidneys when the arterial pressure is elevated, and the increase in urine can actually be as much as five times normal values when the arterial pressure is raised from normal to approximately twice normal. This means that not only can the release of fluid volume from the circulation by way of the kidneys be an important mechanism of arterial pressure regulation but also that it is quantitatively probably one of the most important of them all, despite many protestations to the contrary in the past.

To summarize the hemodynamic response of the kidneys to arterial pressure we can say that they respond to decreased pressure by conserving fluid and salts in the circulation and respond to increased pressure by releasing both fluid and salts from the circulation, thus acting as a negative feedback mechanism operating through changes in blood volume to regulate arterial pressure. Furthermore, the quantitative aspects of this mechanism indicate that it is one of the most important of all the renal mechanisms for control of arterial pressure.

Historically, this hemodynamic concept of renal regulation of arterial pressure preceded all others. However, it gradually fell into disrepute, principally because of the great publicity given to the humoral aspects of renal pressure regulation during the last quarter of a century. Nevertheless, in the absence of humoral factors and even after all nervous reflexes to the kidneys have been completely abrogated by total spinal anesthesia, this hemodynamic mechanism of pressure regulation has still been demonstrated to be very active. Therefore, it cannot be neglected in any analysis of regulation of arterial pressure.

2. Neurogenic Aspects of Renal Arterial Pressure Regulation: The basic hemodynamic response of the kidneys to changes in arterial pressure can be greatly altered by neurogenic reflexes. For instance, sympathetic stimulation increases the pressure level required to cause excessive release of fluid and salts from the circulation.[15] Conversely, reduced sympathetic stimulation allows the kidneys to release slightly increased amounts of fluid and salts.[14] Because the sympathetics are strongly stimulated by pressoreceptor reflexes and especially by the central nervous system ischemic response, we can understand that all the circulatory reflexes help to set the level at which the kidneys regulate arterial pressure. When the arterial pressure falls, thus eliciting a strong pressoreceptor reflex (or in extreme cases of pressure depression eliciting the central nervous system ischemic response), the resultant sympathetic reflexes cause simultaneous decrease in blood flow through the kidneys and consequently decreased renal output. Indeed, a maximal central nervous system ischemic response can actually stop all renal output,[16] thus resulting in complete conservation of fluid and salts in the circulation. In other words, circulatory reflexes not only cause immediate effects in the circulation itself but also cause a more prolonged effect, acting through the kidneys, to promote changes in blood volume that in turn help to regulate the arterial pressure.

A particular example of the neurogenic-renal pressure regulatory mechanism occurs in *acute myocardial infarction*, which often initiates very powerful sympathetic reflexes, so powerful indeed that the arterial pressure itself may not fall a significant amount. Nevertheless, the kidneys often go immediately into an oligemic state because of powerful vasoconstriction of the afferent arterioles to the glomeruli. The retention of fluid and salts that results is almost certainly one of the compensatory mechanisms that allows even the weakened heart to begin pumping increased quantities of blood a few days to a week later. Thus, this neurogenic-renal mechanism is at least one of the pressure regulatory mechanisms in the case of acute myocardial failure.

3. Hormonal and Humoral Mechanisms for Renal-Arterial Pressure Regulation: Many different humoral mechanisms operating in conjunction with the kidneys have been hypothesized as important or in some instances as the most important mechanisms for mean arterial pressure regulation. However, at the present time, only one of these pressure regulating mechanisms has been proved beyond reasonable doubt—the aldosterone-renal mechanism of arterial pressure regulation, which can be described as follows: (A) When the arterial pressure falls very low, such as following acute myocardial infarction or severe hemorrhagic shock, the reduced blood flow through the tissues of the body causes some portion of the diencephalon of the brain to secrete a hormone called *glomerulotropin*.[17] (B) This hormone in turn passes

by way of the blood stream to the adrenal cortices where it enhances the secretion of aldosterone. (C) The aldosterone acts on the renal tubular epithelium to cause absorption of sodium. (D) The absorption of sodium in turn causes water to be reabsorbed from the renal tubules for two different reasons: First, the sodium that has been absorbed into the peritubular fluids acts osmotically to pull water through the tubular membrane. Second, the increased sodium in the extracellular fluids acts on the osmoreceptor system of the supraoptic nuclei and neurohypophysis to cause increased secretion of *antidiuretic hormone*. The antidiuretic hormone then increases the absorption of water from the renal tubules. Thus, aldosterone initiates a sequence of events leading to extreme retention of salt and water, which, in a manner not totally understood, elevates the arterial pressure. This effect is in addition to the hemodynamic and neurogenic-renal mechanisms which have been discussed.

Conversely, an elevation of arterial pressure supplies excess blood to the tissues, resulting in reduced aldosterone secretion and consequently a sequence of events opposite to those just described. Here again, this hormonal-renal mechanism joins with the hemodynamic and neurogenic-renal mechanisms to reduce the blood and interstitial fluid volumes, thereby returning the arterial pressure toward normal.

The renin mechanism for arterial pressure regulation. Beginning in the mid-thirties, it was postulated that kidneys ischemic as a result of low arterial pressure secrete a vasoconstrictor substance called *renin* and that this substance elevates the arterial pressure by constricting the peripheral arterioles throughout the body.[18] When the arterial pressure rises high enough to overcome the ischemia, the kidneys supposedly stop producing renin. Thus, this mechanism would subserve a negative feedback function that could be an effective control system of arterial pressure. Unfortunately, this system still remains a hypothesis because sufficient quantities of renin have never been found in the blood of the normal person to prove the renin mechanism. Most physiologists, therefore, believe that renin plays no essential part in normal regulation of arterial pressure but that it might play a part in the causation of renal hypertension. Indeed, many physiologists are now beginning to believe that renin might not even be involved to any significant extent in renal hypertension. Two particular research studies by Drury have helped to toll the death-knell for this theory. First, it is a well-known fact that renin is a tachyphylactic substance. That is, an initial injection of this substance causes a marked rise in arterial pressure, while each subsequent injection, following at fifteen to thirty minutes intervals, causes progressively less and less rise in pressure. Drury[19] showed that an animal with renal hypertension still becomes tachyphylactic to an injected dose of renin. However, the hypertension persists after tachyphylaxis has developed, illustrating that the animal is totally unresponsive to renin and yet still has hypertension. The hypertension obviously could not be the result of renin because the animal is now unresponsive to this substance. Second, Drury[20] created animals with subtotal aortic coarctation that had hypertension in the upper part of the body but normal pressure in the lower part of the body. In these animals the peripheral arterioles were demonstrated to be greatly constricted in the upper body but normal in the lower body. If the kidney were secreting a vasoconstrictor substance, it should be acting throughout the entire body and not simply in the upper regions. Therefore, it is argued that renin, or any other vasoconstrictor substance for that matter, could not be entering into this differential control of blood vessels in the upper part of the body versus the lower body.

For all these reasons, at the present time, it is almost certain that renin does not play any significant role in normal regulation of arterial pressure, and it is even doubtful that it plays a significant role even in renal hypertension.

Summary

There are two major types of mechanisms by which arterial pressure is regulated, one which opposes acute changes in arterial pressure over a period of seconds, minutes, hours, or days and one which controls the long-term basic level of mean arterial pressure. Among the pressure regulatory mechanisms for keeping the arterial pressure near a normal mean value in acute conditions are (1) the pressoreceptor regulatory system; (2) the central nervous system ischemic reflex system; (3) the stress relaxation mechanism which adapts the vascular dimensions to the blood volume; and (4) the capillary fluid shift mechanism. Long-term regulation of mean arterial pressure, on the other hand, is controlled principally by the kidneys. At pres-

ent, the available research evidence indicates that the kidneys regulate arterial pressure principally by controlling blood volume and the electrolytic constituents of the body fluids. There are three different ways in which the kidneys can regulate blood volume and extracellular electrolytes in response to arterial pressures. These are (1) simple hemodynamic response of the kidneys to changes in arterial pressure; (2) increase and decrease in renal outflow of fluid and salts in response to circulatory nervous reflexes; and (3) increase and decrease in renal output in response to the secretion of aldosterone by the adrenal cortex.

References

1. Kubicek, W. G., Kottke, F. J., Laker, D. J. and Vischer, M. B. Adaption in the pressor-receptor reflex mechanisms in experimental neurogenic hypertension. *Am. J. Physiol.*, 175: 380, 1953.
2. Heymans, C. and Neil, E. Reflexogenic Areas of the Cardiovascular System. Boston, 1958. Little, Brown and Co.
3. Wang, S. C. and Borison, H. L. Analysis of carotid sinus cardiovascular reflex mechanism. *Am. J. Physiol.*, 150: 712, 1947.
4. Guyton, A. C., Batson, H. M., Smith, C. M. and Armstrong, G. G. Method for studying competence of the body's blood pressure regulatory mechanisms and effect of pressoreceptor denervation. *Am. J. Physiol.*, 164: 360, 1951.
5. Britton, S. W. Comparative effects on the circulatory system of positive and negative accelerations: the "Marey" law. *Am. J. Physiol.*, 156: 1, 1949.
6. Sagawa, K., Ross, J. and Guyton, A. C. Quantitation of the cerebral ischemic pressor response in dogs. *Am. J. Physiol.* In press.
7. Alexander, R. S. Elasticity of muscular organ In: Remington, J. W. Tissue Elasticity, pp. 111–122. Washington, D. C., 1957. American Physiological Society.
8. Remington, J. W. Tissue Elasticity, pp. 138–53. Washington, D. C., 1957. American Physiological Society.
9. Guyton, A. C. and Crowell, J. W. The heart in shock. (Part of a symposium of the National Research Council.) *Fed. Proc.* In press.
10. Guyton, A. C., Batson, H. M., Jr., and Smith, C. M., Jr. Adjustments of the circulatory system following very rapid transfusion or hemorrhage. *Am. J. Physiol.*, 164: 351, 1951.
11. Shirley, H. H., Jr., Wolfram, C. G., Wasserman, K. and Mayerson, H. S. Capillary permeability to macromolecules: stretched pore phenomenon. *Am. J. Physiol.*, 190: 189, 1957.
12. Wolcott, W. W. Blood volume in experimental hemorrhagic shock. *Am. J. Physiol.*, 143: 247, 1945.
13. Wolf, A. V. Thirst. Springfield, Illinois, 1958. Charles C Thomas.
14. Langston, J. B., Guyton, A. C. and Gillespie, W. J. Acute effect of changes in renal arterial pressure and sympathetic blockade on kidney function. *Am. J. Physiol.*, 197: 595, 1959.
15. Langston, J. B. and Guyton, A. C. Effect of epinephrine on the rate of urine formation. *Am. J. Physiol.*, 192: 131, 1958.
16. Guyton, A. C., Scanlon, L. J. and Armstrong, G. G. Effect of pressoreceptor reflex and Cushing reflex on urinary output. *Fed. Proc.*, 11: 61, 1952.
17. Rauschkolb, E. W. and Farrell, G. L. Evidence for diencephalic regulation of aldosterone secretion. *Endocrinology*, 59: 526, 1956.
18. Blalock, A. Experimental hypertension. *Physiol. Rev.*, 20: 159, 1940.
19. Drury, D. R. and Schapiro, S. Renin tachyphylaxis and renal ischemia in the cat. *Am. J. Physiol.*, 187: 520, 1956.
20. Drury, D. R. Personal communication.

Case Reports

Unusual Effects of Chronic Myocarditis*

JAN SZATKOWSKI, M.D., SECUNDINO VEIGA, M.D., HOWARD WEISS, M.D. *and* JOSEPH H. YAHINI, M.D.†
Chicago, Illinois

THE CLINICAL and instrumental diagnosis of myocarditis may at times be difficult, as proved by an unusual case under our observation.

CASE REPORT

HISTORY

M. T., a fourteen year old Jewish boy from Tel Aviv, Israel, was admitted to Mount Sinai Hospital, Chicago, on August 26, 1959. He was apparently in good health until about five years of age. At five and six years of age, he had an attack of pneumonia each year, from which he recovered. At age seven he had an attack of fainting which was diagnosed by a physician as a "heart attack." From that time chronic anorexia developed and he had intermittent episodes of syncope, and growth was markedly retarded. For the last two years he had progressive exertional dyspnea, chronic cyanosis and generalized weakness. His physical activity was limited and he was able to walk only short distances.

Medical investigation in Tel Aviv two years previously revealed the presence of an apical systolic murmur and a questionable apical diastolic murmur which was said to disappear later. One year prior to admission cardiac catheterization was performed, followed in two weeks by development of right hemiplegia and aphasia which resolved in about three weeks. This study failed to reveal the presence of a shunt but did reveal severe right ventricular and pulmonary hypertension and high wedge pressure. The investigators were unable to make any definitive cardiac diagnosis. The patient had received digitalis for a long period of time. He had also received a course of cortisone during the past year. However, due to a progressively deteriorating course, he was sent to Mount Sinai Hospital for further cardiac studies and possible treatment.

PHYSICAL EXAMINATION

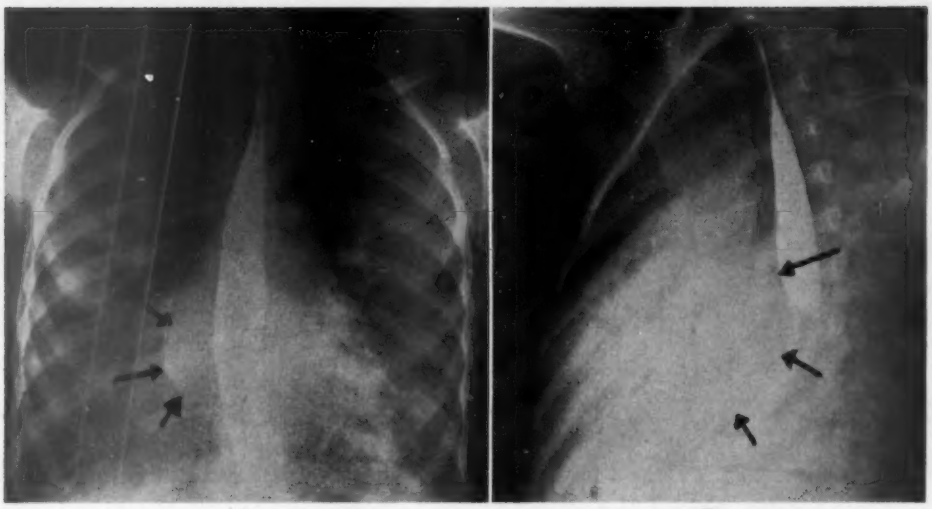
The patient was an underdeveloped, poorly nourished, adolescent boy who appeared younger than his chronologic age of fourteen years. His weight was fifty-six and a half pounds and his height was fifty inches, both of which are far below the third percentile for his age.

He was afebrile. The pulse was 120 per minute; respiration was 40 per minute and moderately labored. Blood pressure was 100/70 mm. Hg in the upper extremities but was difficult to obtain in the legs. By palpation of the dorsal pedis pulse, the systolic pressure of the artery was obtained at 64 mm. Hg. The patient was pale with a slight cyanotic hue; he was orthopneic and always appeared uncomfortable. There was flaring of the nostrils and the cervical veins were engorged.

Cardiac findings revealed a slight left precordial bulge, no thrill and the maximal impulse palpable in the left fifth intercostal space 1 cm. outside the nipple line. The first sound was normal, loudest at the apex; the second sound was widely split over the left second interspace with a very loud pulmonic component; a triple rhythm was heard at times over the apex. No significant murmur was audible. Fine crepitant râles were heard posteriorly in both lungs. The liver was palpable 2 cm. below the costal margin and was firm. No peripheral edema was noted. The femoral pulses were palpable but weak.

Clinical Course: While cardiac investigation was being carried out the patient was treated with increased dosage of digoxin, intermittent oxygen and chlorothiazide. During the first five days, his clinical condition was improved somewhat. On the sixth day after admission right and left heart catheterizations were performed. Following these studies the patient became more dyspneic and apprehensive and vomited several times. Subsequently, he appeared more comfortable. Seven days later left heart catheterization was repeated. Soon after termination of the procedure cardiac arrest occurred. The patient was treated with repeated tapping of the precordium, oxygen, norepinephrine and niketh-amide (Coramine®) and recovered after about

* From the Division of Cardiology, The Chicago Medical School and Mount Sinai Hospital, Chicago, Illinois.
† Present address: Petah Tiqvah, Israel.



A B

FIG. 1. *Teleoroentgenograms.* A, posteroanterior view with barium swallow. The left atrium is clearly visible as a round shadow at the center of the heart (arrows). B, lateral view with barium swallow. The left atrium is clearly visible showing a severe bulge (arrows), and producing retrodisplacement of the esophagus.

twenty minutes. Following this episode, a left hemiparesis developed; the patient gradually improved with the aid of physical therapy.

LABORATORY DATA

Complete blood count, urinalyses, blood chemistry determinations, sedimentation rate, antistreptolysin-O titer, C-reactive protein and three lupus erythematosus preparations were all within normal limits.

X-ray Examination: The posteroanterior view of the chest revealed a moderately enlarged heart with rounded apex and bulging of the pulmonic segment (Fig. 1). A concentric shadow was noted within the right cardiac silhouette indicating a severely enlarged left atrium. Marked pulmonary congestion was noted in some of the films. In the left anterior oblique view with barium there was compression of the esophagus by the dilated left atrium. Thus, the x-ray study revealed *a moderately enlarged heart with marked sectional enlargement of the left atrium and right ventricle.*

Electrocardiography: The electrocardiogram (Fig. 2) showed sinus rhythm, no axis shift, notched P in lead I and tall P in II, aVF and V_1. There were polyphasic QRS complexes in several leads and depressed S-T in all leads excepting III and aVR. Low or inverted T waves were noted in all leads. *Conclusions:* The interpretation was: digitalis effect, diffuse myocardial damage, distention or damage of both atria, and right ventricular hypertrophy.

Angiocardiography: This procedure was performed at the Cook County Children's Hospital Cardiovascular Department under the direction of Dr. B. M. Gasul (Fig. 3). A *dextroangiogram* at four seconds showed the following: posteroanterior view revealed enlarged right atrium and ventricle, normal pulmonary infundibulum and marked enlargement of the main pulmonary artery; lateral view revealed anterior enlargement of the right ventricle and tremendous enlargement of the pulmonary artery. A *levoangiogram* at fifteen and a half seconds (Fig. 3A and B) showed the tremendously enlarged left

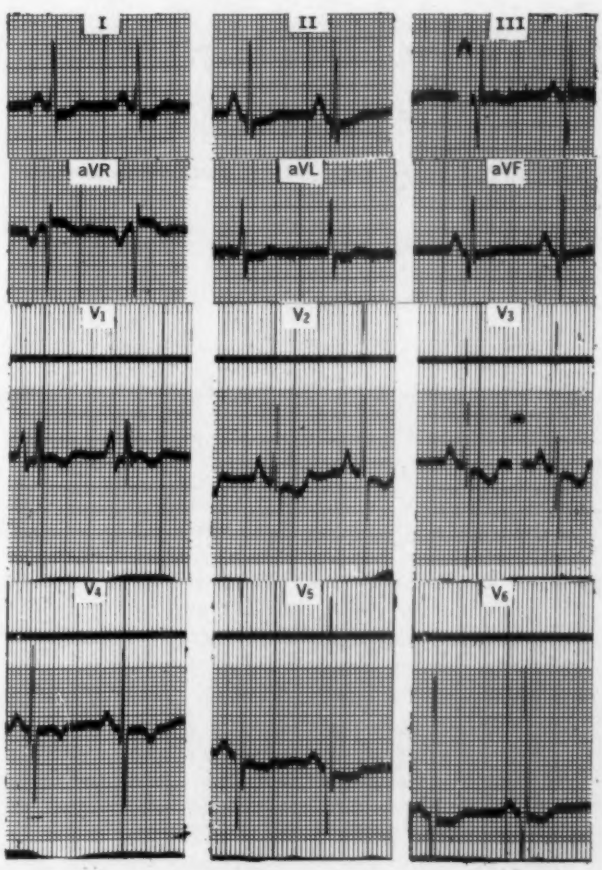
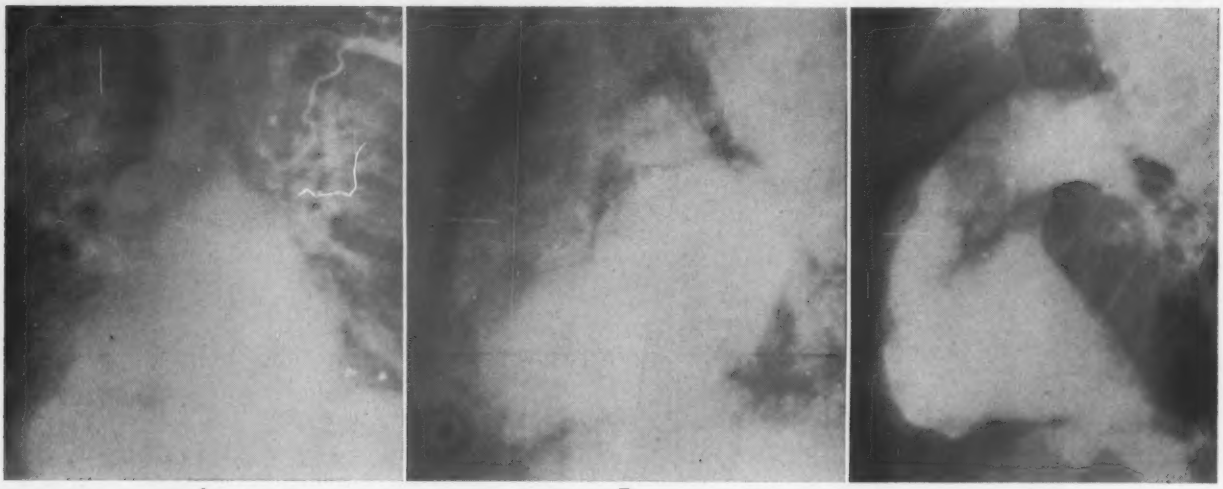
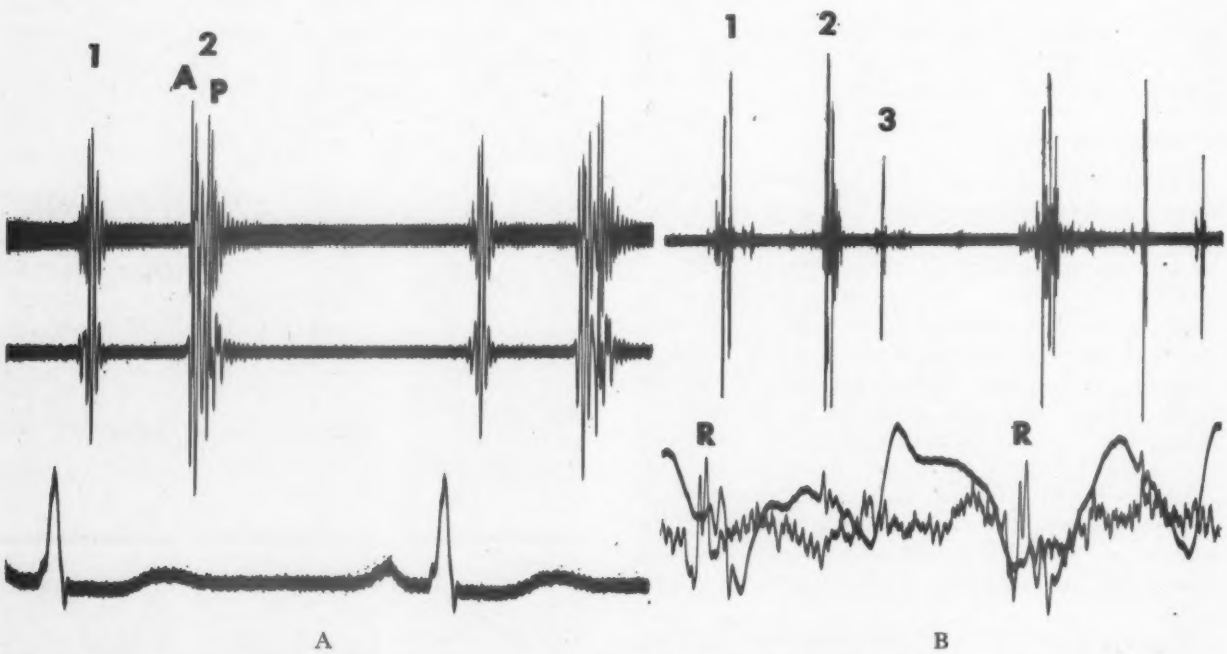


FIG. 2. *Electrocardiogram* of the patient (see text).



A B C

FIG. 3. *Angiocardiograms.* A, anteroposterior projection shows the marked enlargement of the left atrium. The left ventricle is not enlarged. There are more prominent vascular markings in the upper lung fields. B, lateral view showing the enormous enlargement of the left atrium. C, lateral view showing opacification of the left ventricle and aorta; the right ventricle still contains contrast medium.



A B

FIG. 4. *Phonocardiograms.* A, over pulmonic area, showing the splitting of the second sound. B, at the apex, showing the triple rhythm due to ventricular gallop. Electrocardiogram (muscular tremor); apex cardiogram.

atrium in the posteroanterior and lateral views; the left ventricle did not appear enlarged. At this late time the pulmonary artery was still visualized, indicating delayed pulmonary blood flow. The left atrium was still filled on many films, indicating slow emptying of this chamber.

Phonocardiography: No murmur was recorded. The second sound was split (Fig. 4A). A large vibration at the apex in early diastole was interpreted as a third sound (triple rhythm) (Fig. 4B).

Left and Right Heart Catheterization: Right heart catheterization revealed moderate pulmonary hypertension: pulmonary artery pressure, 53/32 mm. Hg; right ventricular pressure, 50/9 mm. Hg; wedge pressure, 18 mm. Hg (Fig. 5A). Cardiac output was very low, only 1,400 cc. per minute. There was no evidence of a shunt. *Left heart catheterization* revealed a very high pressure in the left atrium, 27/21 mm. Hg. Left ventricular pressure was 93/21 mm. Hg. No pressure gradient was found between the left atrium and left ventricle by recording simultaneous tracings (Fig. 5B). Isoproterenol was injected as a diagnostic test. The tachycardia caused by this drug failed to create a pressure gradient across the mitral valve.

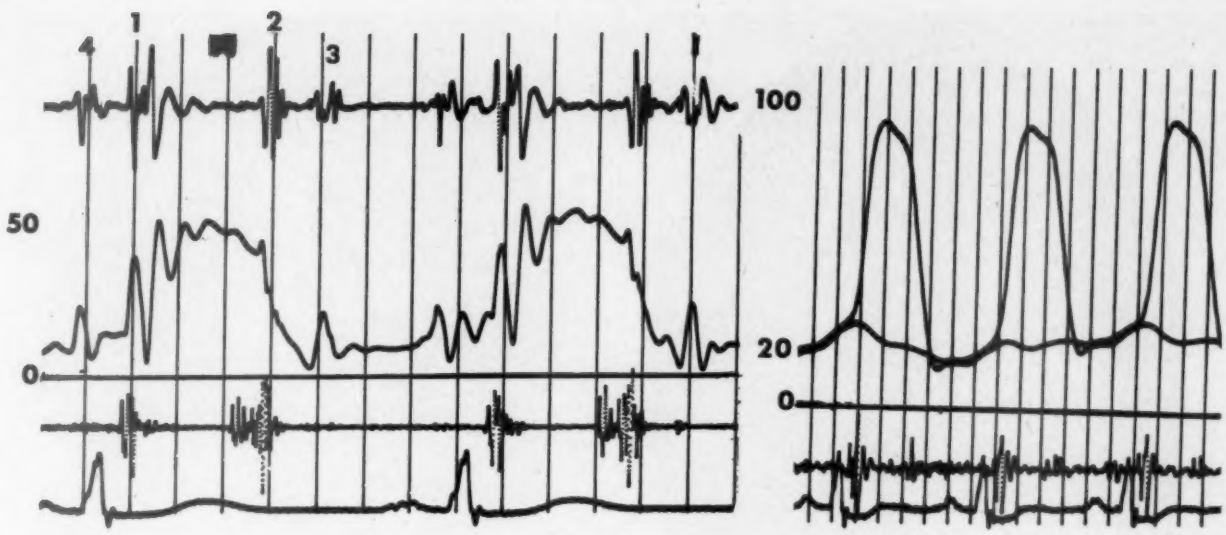


FIG. 5. A, *right heart catheterization,* right ventricular tracing. *From above:* Intracardiac phonocardiogram showing four heart sounds; right ventricular pressure tracing showing exaggeration of waves of rapid filling and presystolic filling; external phonocardiogram showing that the second component of the second sound is a pulmonic component; electrocardiogram. B, *left heart catheterization.* Simultaneous pressure tracings of the left ventricle and left atrium. *Below:* external phonocardiogram and electrocardiogram. There is no gradient of pressure across the mitral valve.

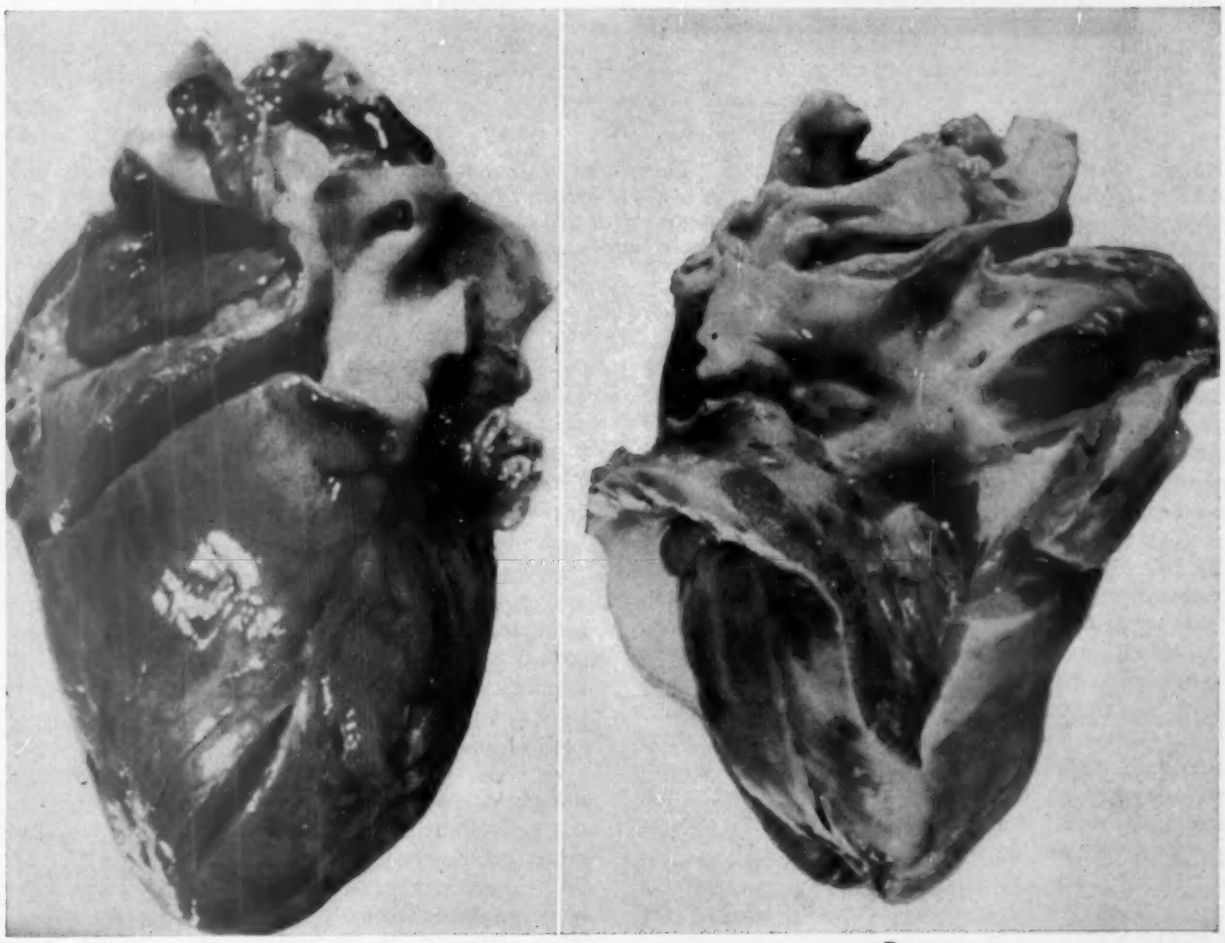
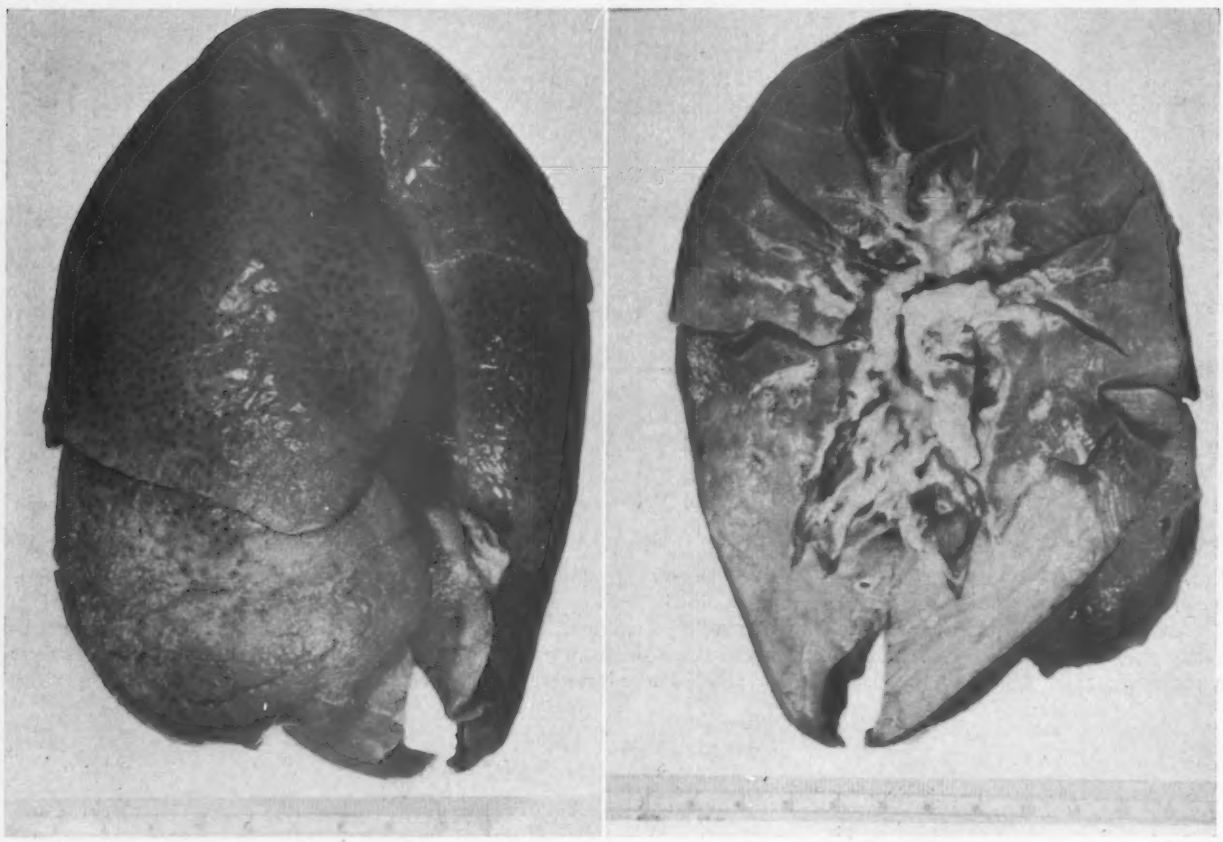


FIG. 6. *Gross appearance of heart.* A, anterior view. Note the comparatively small left ventricle. B, evidence of right ventricular hypertrophy.



A B

FIG. 7. *Gross appearance of lungs.* A, right lung. The pleura of the lower portions of the lung appears rough and thickened. B, cut section of the pulmonary parenchyma to illustrate the diffuse induration of the lower portions and the geographic appearance of the fibrosis in the middle third. At the apex, the interstitial fibrosis is less pronounced, although conspicuous. Note the homogeneous glossy appearance and the absence of grossly aerated parenchyma throughout.

SURGICAL FINDINGS

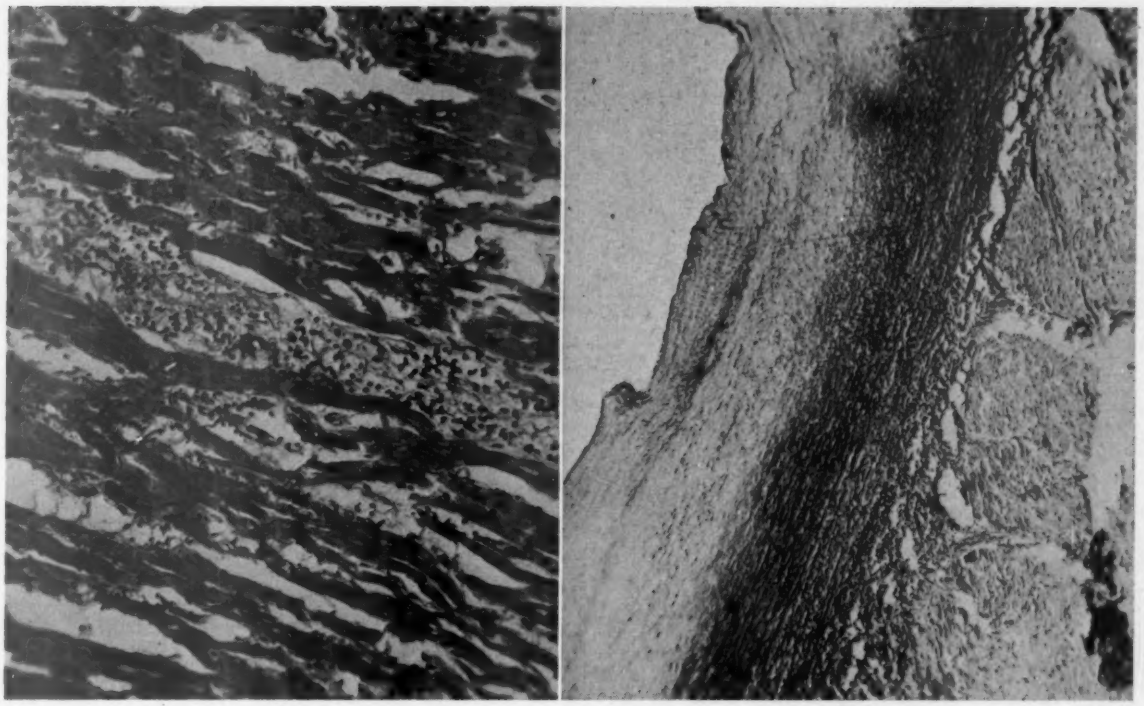
Because of the difficulty in arriving at a definitive diagnosis and the fact that an obstructive lesion in the region of the mitral valve could not be absolutely ruled out, and because the patient's condition was rapidly deteriorating with no hope of improving with existing medical management, it was decided to perform a thoracotomy for the purpose of exploring the mitral valve, and, if it were normal, obtaining a biopsy specimen of the left ventricular muscle. On October 6, 1959, Dr. E. Fell performed the operation. He noted that the lower lobes of the lungs were extremely fibrotic and liver-like in consistency. On exploring the mitral valve he could not actually feel the leaflets. There was no obstruction in the mitral ring. As he was exploring the valve, cardiac standstill developed. Cardiac massage and resuscitation measures were unsuccessful and the patient was pronounced dead on the table.

POSTMORTEM FINDINGS

GROSS EXAMINATION

The heart weighed 270 gm. (Fig. 6). The epicardium was smooth and there was a recent incision in the left auricular appendage sutured with silk. The myocardium was reddish-brown and somewhat firm. There was marked hypertrophy and dilatation of the right ventricle. The right ventricular wall measured 1 cm. in thickness. The wall of the left ventricle measured 1.2 cm. in thickness, the myocardium was firm and *there was no significant dilatation of this chamber. Both atria were markedly dilated, particularly the left.* The atrial endocardium was thickened, dull glossy and whitish throughout. These changes were more pronounced on the left. The mural endocardium of the ventricles showed discrete focal patches of thickening and whitish discoloration. The valves were not remarkable.

The right lung weighed 440 gm. and the left 350 gm. (Fig. 7A). The pleural surfaces were dull and thickened, particularly in the lower portions. On cut section, the parenchyma was firm throughout but more prominently in the lower lobes (Fig. 7B). Both lower lobes and the middle lobe of the right lung were grayish-white and gritty, the upper lobes appeared grayish-brown and congested. The small branches of the pulmonary arteries showed multiple foci of atheromata.



A B

FIG. 8. *Microscopic sections of heart.* A, myocardium of the left ventricle showing focus of active chronic myocarditis. (Hematoxylin and eosin stain; original magnification ×110.) B, left atrial endocardium. Note the thickening of the endocardium and the increased number of elastic fibrils. (Verhoeff's elastic strain; original magnification ×32.)

The liver weighed 1,020 gm. The surface was slightly nodular. On cut section the parenchyma was firm, discretely nodular, brownish and mottled. The *spleen* weighed 150 gm.; its capsule was smooth and, on cut section, the pulp was dark red. Coronal sections of the *brain* revealed a cystic area of encephalomalacia on the left side extending from the region of the claustrum and lateral part of the lentiform nucleus into the internal capsule, just before the genu.

MICROSCOPIC EXAMINATION

Heart: Sections showed scattered areas of *interstitial fibrosis* with fragmentation of the myocardial fibers (Fig. 8A). In these areas, there were variable numbers of *chronic inflammatory cells*, particularly lymphocytes and occasional plasma cells. Anitschkow myocytes were also conspicuous. The endocardium, particularly in the left atrium, was thickened due to proliferation of fibrocollagenous tissue and elastic fibrils (Fig. 8B).

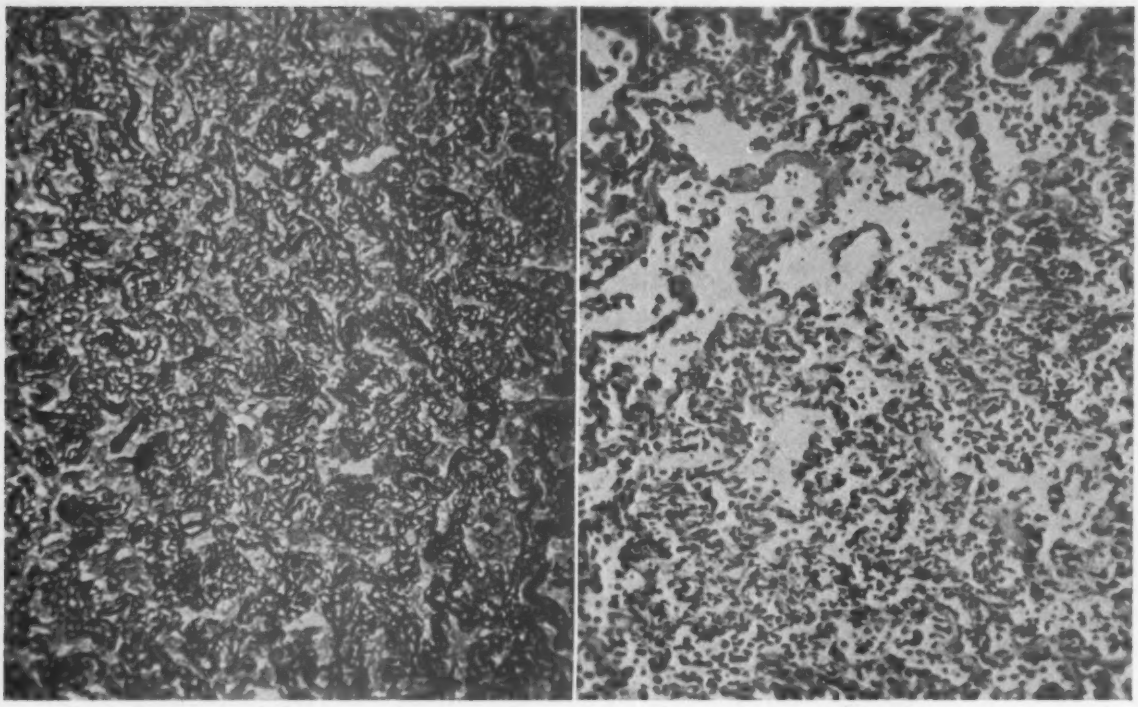
Lungs: Microscopic examination of the lower lobes revealed a *rather diffuse interstitial fibrosis* which was variable in degree but present throughout (Fig. 9A). In some areas the fibrous tissue was densely collagenous with little inflammatory reaction (Fig. 9B). In others, the connective tissue was loose and round cell infiltration was more pronounced. Proliferation of smooth muscle bundles was seen in the areas of fibrosis. The peribronchial smooth muscle bundles appeared hyperplastic, particularly around the smaller bronchi. The alveolar spaces appeared collapsed and the alveolar septa were thickened. Many air spaces contained groups of macrophages, some of which were laden with hemosiderin. Sections from the upper lobes revealed a similar picture, except that the interstitial fibrosis was somewhat less pronounced.

Liver: Histologic examination showed irregular fibrosis with large areas of centrolobular congestion and necrosis. The lobular pattern was distended and some evidence of septation was present; in many areas the sinusoids were distended.

Brain: Sections from the left internal capsule revealed an old focal area of cystic encephalomalacia.

PATHOLOGIC DIAGNOSIS

Diagnosis was: diffuse chronic interstitial pulmonary fibrosis, similar to that described in the Hamman-Rich syndrome, with an added component of chronic passive congestion; *interstitial myocarditis with fibrosis*, focally active and predominant on the left side; *secondary fibroelastosis* plus hypertrophy and dilatation of the left atrium; moderate hypertrophy and dilatation of the left ventricle; severe right ventricular hypertrophy and dilatation, similar to that of chronic cor pulmonale; and old focal encephalomalacia of left internal capsule.



A B

FIG. 9. *Microscopic sections of lungs.* A, lower lobe showing marked thickening of the alveolar septa and increase in the reticulum fibers. Note the compressed alveolar spaces. (Snook's reticulum stain; original magnification ×110.) B, upper lobe showing an area of less pronounced interstitial fibrosis. Toward the center of the section there are a few distended air spaces in contrast to the peripheral areas in which the collapsed alveoli predominate. Note groups of alveolar macrophages. (Hematoxylin and eosin stain; original magnification ×110.)

COMMENTS

This patient came to us with a difficult clinical problem. He was a remarkably underdeveloped adolescent boy with chronic congestive heart failure, a moderately enlarged heart, no murmurs, and presenting a tremendously enlarged left atrium.

X-ray examination and angiocardiography confirmed these data and showed the following: (1) the evidence of pulmonary lesions; and (2) the remarkable difference in size between a practically normal left ventricle and the enormous left atrium.

The data from catheterization were extremely significant. They revealed marked right ventricular and pulmonary hypertension; high wedge and left atrial pressures; no gradient across the mitral valve; and a high diastolic pressure within the left ventricle. The absence of a mitral valve gradient seemed to exclude mitral stenosis. The pressure patterns within the left ventricle and atrium were normal, thus excluding mitral insufficiency. Catheterization also revealed that there were no left to right shunts.

Primary interstitial pulmonary fibrosis, or Hamman-Rich syndrome, was considered. However, this did not seem consistent with the catheterization data. A diffuse Hamman-Rich syndrome causes a chronic cor pulmonale; namely, an extremely high pressure in the right ventricle and pulmonary artery and a normal or low pressure in the pulmonary capillaries (wedge) and left atrium. It was further apparent that there was a combination of facts indicating: (1) a left heart lesion (possible mitral stenosis, fibroelastosis or left ventricular failure); and (2) a lesion of the pulmonary vessels.

Therefore, attention was concentrated on the consistently elevated level of pressure from the left ventricle (diastole) to the atrium, to the pulmonary artery and right ventricle. This pattern has become known as a *plateau pattern* and has been noted in several conditions preventing normal diastolic filling of the left heart such as constrictive pericarditis, amyloid disease or fibroelastosis. The same pattern has also been found occasionally in left ventricular fibrosis or myocarditis with chronic left ventricular failure. However, these conditions are

usually associated with left ventricular enlargement, which was not present in this patient. Therefore, even though these diagnoses were considered, none was definitely admitted as the main cause of the syndrome. Fibroelastosis was discussed at length. Finally, it was excluded by the pathologist as the cause of the syndrome (fiibroelastosis of the left atrium was considered as a secondary process). This case teaches that chronic myocarditis and myocardial fibrosis of the left ventricle *can* cause a plateau level of pressures of long duration. A similar conclusion was reached in a study by Burwell and Brown.[1]

In regard to the etiology of the case, we can only speculate. The patient had a history of two episodes of pneumonia at five and six years of age. These were probably of an interstitial variety, possibly of virus etiology. The patient probably had an acute myocarditis associated with these episodes. The myocarditis and interstitial pneumonitis never healed but remained active, going into fibrosis. The fainting episode at age seven was probably associated with the first episode of congestive failure. From that time on the boy apparently remained in chronic failure which became progressively more disabling.

The findings in the left side of the brain reveal that there had been an embolism at the time of the first episode of right hemiparesis. On the other hand, the more recent episode of left hemiparesis was unaccompanied by evident lesions and was probably connected with hypoxia which occurred at the time of cardiac arrest.

Summary

A case of chronic myocarditis complicated by extensive pulmonary fibrosis is presented. The chronic inflammatory process, predominantly located in the left ventricle, raised the diastolic pressure of this chamber, contributed to a remarkable distention of the fibrotic left atrium and of the right heart.

The case was completely studied by angiocardiography and right and left heart catheterizations. The lack of a mitral gradient had excluded mitral stenosis. However, the lack of left ventricular dilatation, at least from a clinical point of view, had been held against the diagnosis of myocarditis.

Autopsy disclosed an extensive chronic myocarditis and a process of chronic fibrosis of the lungs. The extreme dilatation of the left atrium, the severe elevation of the left atrial pressure, and the proportionate increase of right ventricular pressure ruled against a significant contribution of the pulmonary process to the right ventricular overload (possibly because several areas of the lungs were less involved).

Thus, it is evident that the finding of a "plateau" level of pressure behind the left ventricle, similar to that caused by rigidity of the left ventricular wall, does not exclude chronic myocarditis.

The pulmonary and myocardial process is tentatively explained as the result of an old viral infection.

Acknowledgment

The authors wish to thank Drs. Aldo A. Luisada and Leo Krainer for their criticisms and collaboration.

Reference

1. Burwell, C. S. and Brown, R. D. Diagnosis of diffuse myocardial fibrosis. *Circulation*, 20: 606, 1959.

Alveolar Hypoventilation and Cor Pulmonale Secondary to Damage to the Respiratory Center*

RICHARD L. NAEYE, M.D.

Burlington, Vermont

CLINICAL AND physiologic studies suggest that in some patients who are refractory to the usual chemical stimuli to ventilation, there may be organic injury to the medullary respiratory center.[1–10] Alveolar hypoventilation and arterial hypoxemia with evidences of pulmonary arterial hypertension and cor pulmonale develop in these persons. However, actual organic disease of the medullary respiratory center has been demonstrated only in patients who died of bulbar poliomyelitis.[10–12] The present case report includes autopsy findings of damage to the respiratory center in a patient with alveolar hypoventilation whose illness was not attributable to poliomyelitis. Abnormalities were also noted in the pulmonary vascular bed which help to explain the development of pulmonary arterial hypertension.

CASE REPORT

J. P., a thirty-eight year old laborer, was admitted to Presbyterian Hospital, New York City, on October 16, 1957 with a history of ten days of drowsiness and cyanosis. He was well until three months before admission when a nonproductive cough developed which increased in severity and frequency despite cessation of cigarette smoking. He noted slight dyspnea on exertion about five weeks before admission. Soon after this he began to doze on the job. He was given amphedrine by his family physician but experienced little relief of his somnolence. Seven days before admission he was admitted to another hospital with the presumptive diagnosis of viral pneumonia. While there he became stuporous and markedly cyanotic. The concentration of carbon dioxide in his serum was 64 mEq. per L. He had an ineffective cough and could not clear his pharyngeal secretions. Because of stupor he was admitted to the Presbyterian Hospital, three days before death.

On admission, he appeared acutely ill with marked, generalized muscular weakness, obtundity and prominent cyanosis. His temperature was 102.3°C. His breathing was shallow and irregular; his respiratory frequency was 24 per minute. The pulse rate was 124 per minute; the blood pressure 124/86 mm. Hg. The eye grounds were within normal limits except for venous congestion. Scattered rhonchi were audible throughout both lung fields. The heart appeared enlarged to percussion and the second pulmonic sound was abnormally loud. The edge of the liver was palpated 2 fingerbreadths below the right costal margin and there was slight pitting edema of the ankles. Except for generalized weakness and obtundity the neurologic examination was not remarkable.

Initial laboratory examination showed a hematocrit of 52 per cent and a white cell count of 8,900 per cu. mm. with a normal differential. The blood glucose was 198 mg. and the nonprotein nitrogen 39 mg. per 100 ml.; the serum CO_2 was 55 mEq.; chloride, 85 mEq.; potassium, 5 mEq.; and sodium, 142 mEq. per L. Urinalysis revealed a trace of protein. The venous pressure was 129 mm. H_2O. The spinal fluid pressure was elevated to 370 mm. H_2O; otherwise, the spinal fluid contained normal concentrations of protein, sugar and chloride and its leukocyte count was not elevated. The blood culture had no growth; the sputum culture contained predominantly staphylococcus aureus. The x-ray film of the chest revealed pulmonary congestion. The electrocardiogram revealed prominent P waves in leads II and III with low P waves in lead I as seen in cor pulmonale.

Treatment: On admission myasthenia gravis was considered to be a possible cause of his respiratory difficulty but no appreciable improvement followed the injection of either neostigmine (Prostigmine®) or atropine. His difficulties were then recognized to arise from carbon dioxide narcosis which, in turn, arose from alveolar hypoventilation. Because of the possibility of an inapparent respiratory infection he was treated with penicillin and chloramphenicol. He also received injections of caffeine to stimulate his respirations. Following these injections, the respira-

* From the Department of Pathology, The University of Vermont, College of Medicine, Burlington, Vermont.

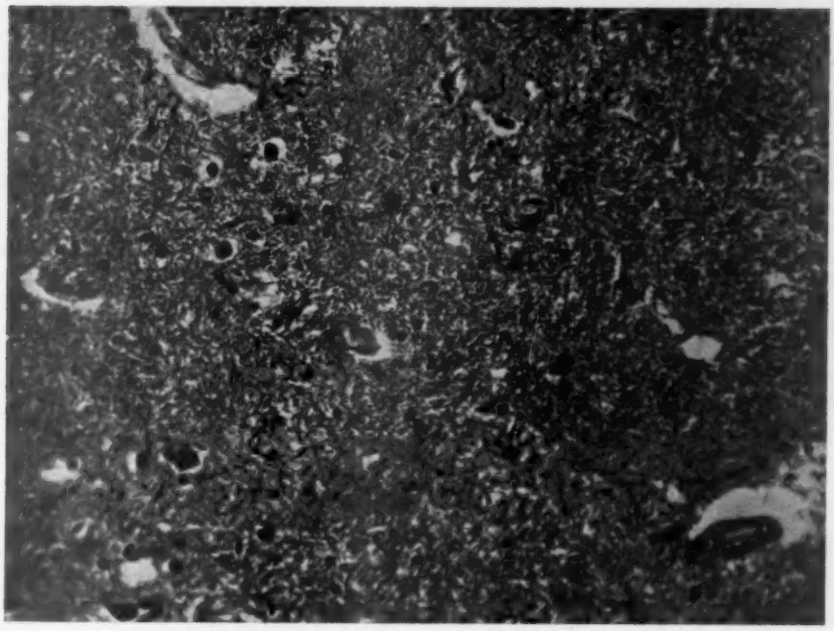


FIG. 1. Low power view of the nucleus cuneatus in the medulla oblongata showing a diffuse loss of ganglion cells with reactive gliosis.

tions increased in depth, cyanosis virtually disappeared and he became more alert. An intermittent positive pressure breathing apparatus (Emerson Company) was used to sustain the increased ventilation. During its use and while on regular injections of caffeine, the serum CO_2 was 41.8 mEq. per L. and the systemic arterial oxygen saturation was 91 per cent.

In the middle of the first night hematemesis began; it continued over the next fifteen hours so that his hematocrit dropped to 46 per cent despite infusion of 1,500 cc. of whole blood. Shortly thereafter laryngospasm developed. Attempts to establish a patent airway were unsuccessful and the patient died.

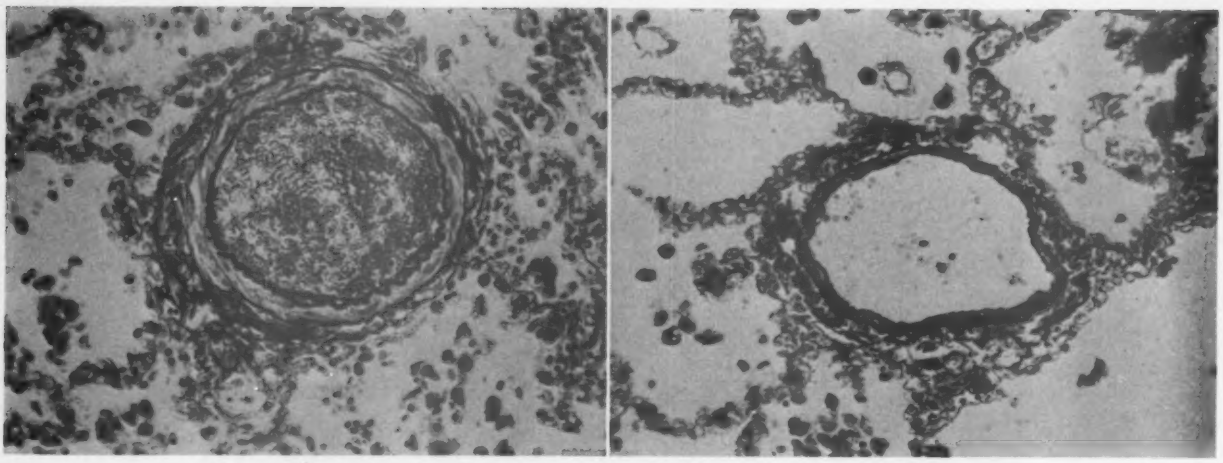
POSTMORTEM EXAMINATION

At autopsy twelve hours after death, the body was that of a well developed and well nourished man measuring 167 cm. in length. All skeletal muscle was red-brown and firm. About 150 cc. of clear fluid was present in each pleural space. The enlarged heart weighed 500 gm. The right ventricle was dilated and hypertrophied with an average thickness of 0.6 cm. No other cardiac chamber was either dilated or hypertrophied. The myocardium was firm and of a normal color. There were no valvular abnormalities or unusual communications between the cardiac chambers. The left lung weighed 610 gm. and the right 630 gm. The bronchi contained some brownish, blood-tinged material and their underlying mucosa was reddened. Palpation of both lungs revealed scattered firm areas in which crepitations were reduced. The main pulmonary arteries were somewhat dilated but had no atheromatous plaques or evidence of antemortem thrombi. Injection of the arteries with a gelatin preparation[13] gave no evidence of an abnormal arteriovenous communication. Cultures of the lungs grew Asian influenza virus and a few colonies of pyocyaneus.

The liver was enlarged, weighing 2,100 gm. It had a faint yellow cast. The stomach contained 100 ml. bloody, clotted material. No ulceration was demonstrated. The remainder of the gastrointestinal tract was free of gross abnormalities.

Microscopically, the heart was normal except for hypertrophy of the myocardial fibers of the right ventricle. The lungs showed mild capillary congestion and protein-containing fluid in the alveoli. There were no hyaline membranes. Acute bronchitis and bronchiolitis as well as patchy areas of acute lobular pneumonia were present. There was no parenchymal fibrosis or other evidence of any chronic pulmonary disease. Small quantities of fat were found in hepatic parenchymal cells. Bone marrow showed a moderate myeloid and normoblastic erythroid hyperplasia.

Central Nervous System: Although the brain was not remarkable on gross examination, extensive lesions were displayed on microscopic examination. Many areas of the brain showed vascular congestion. Veins in one corpus mammillare were dilated with focal necrosis in the surrounding tissue. In the substantia nigra, there was a paucity of nerve cells and many of the remaining cells were shrunken. Occasional cells contained one or more rounded, dense, eosinophilic cytoplasmic inclusions surrounded by a clear halo which resembled the inclusions sometimes seen in paralysis agitans. These lesions in the substantia nigra were judged to be old and degenerative in character. Focal losses of nerve cells were also found throughout the midbrain, pons and walls of the pos-



A B

FIG. 2. A, representative muscular artery from the upper lobe of the right lung. It is dilated as indicated by straightening of the internal elastic membrane. Its medial smooth muscle coat is much thicker than that of a similar artery. B, muscular artery from the upper lobe of a control subject matched for age.

terior portion of the third ventricle with resultant microgliosis and increase in the number of capillaries.

Special attention was given to the medulla, which is generally held to contain the respiratory center. Lesions in this area were diffuse. There was a reduction in nerve cells in the reticular formation with a reactive proliferation of microglia and astrocytes. Changes were similar in the floor of the fourth ventricle, dorsal vagus nuclei, medial vestibular nuclei, nucleus solitarius and other nuclei (Fig. 1). There was a mild increase in the number of capillaries. These lesions in the medulla were judged to be subacute to chronic. There was also a mild degeneration and disappearance of anterior horn cells in cervical and lumbar enlargements of the spinal cord.

SPECIAL STUDIES OF PULMONARY VASCULATURE

The pulmonary vascular bed was studied in an attempt to determine the cause of the hypertrophy of the right side of the heart, i.e., chronic cor pulmonale. Tissue blocks from all lobes of both lungs were sectioned serially and stained with Verhoeff's and Van Gieson's stains. No thrombi or emboli were found in any of the vessels. All forms of vasculitis were absent. No intimal or elastic membrane abnormalities were found in any of the vessels. The smooth muscle coat of the arteries and arterioles was quantified by a special technic.[14] The mean muscle mass of the pulmonary arterial bed in this case was found to be 2.3 times that found in comparable arteries of normal control subjects (Fig. 2). The increase was distributed about arterioles and arteries of all sizes, being very evident in the smaller vessels where the bulk of pulmonary vascular resistance probably lies. Other measurements revealed that pulmonary arteries of all sizes were dilated to about three times the normal size.[18] No structural abnormalities were found in pulmonary veins or in bronchial vessels. No abnormal communications were found between pulmonary arteries and veins either by the injection or serial section studies.

COMMENTS

This patient represents an instance of alveolar hypoventilation secondary to organic disruption of the medullary respiratory center. Such damage to the respiratory center has been postulated previously to account for the occurrence of similar clinical syndromes. Heretofore, however, the opportunity for anatomic examination of the brain has been possible only in instances of bulbar poliomyelitis.[10–12]

There was little evidence in the present patient to implicate poliomyelitis. In this case, extensive lesions were found in the reticular substance of the medulla where the respiratory center is thought to be located.[10–12,15,16] It is postulated that this organic damage was responsible for an insensitivity of the respiratory center to carbon dioxide which culminated in alveolar hypoventilation and hypercapnia. Once hypercapnia was established, functional insensitivity of the respiratory center was added to the organically induced refractory state.[7] It is likely that only the functional component of this depression responded to the administration of caffeine and picrotoxin with a marked ventilatory response. In other reported cases caffeine, lobeline and salicylate failed to increase minute ventilation although in one instance aminophylline was effective.[5,6,8]

The patient's systemic hypoxemia was undoubtedly related to alveolar hypoventilation from the brain stem injury since there were no changes in the lungs or heart which might other-

wise explain this abnormality. An alternate explanation for the hypoxemia, pulmonary arteriovenous fistula, was thought unlikely on two accounts: (1) the cyanosis disappeared with augmented minute ventilation; and (2) we were unable to disclose such an abnormal communication by postmortem injection of the pulmonary vascular tree.

Many hemodynamic features of the case can be related to the arterial oxygen unsaturation: (1) pulmonary hypertension which is common in patients with arterial hypoxemia can account for the hypertrophied right side of the heart; (2) the hypertrophy of pulmonary arterial smooth muscle is similar to that seen in other persons with pulmonary arterial hypertension due to hypoxemia[17–18]; and (3) dilatation of the pulmonary arterial bed may arise from the augmented pulmonary blood volume which accompanies secondary polycythemia.[17–18]

The present study did not disclose the etiology of the cerebral changes. Although Asian influenza virus was recovered from the lungs, the cerebral lesions were unlike those reported with encephalitis due to this agent.[19] In fact, the lesions could not be related to any form of encephalitis since inflammatory changes were absent. There was some resemblance to lesions seen in certain metabolic and nutritional disorders such as Wernicke's encephalopathy but other evidences of such disturbances were lacking.

Summary

A patient is described with alveolar hypoventilation due to organic disease of the brain in whom cor pulmonale developed. Lesions were found in the portion of the medulla where the respiratory center is thought to be located. As a consequence of alveolar hypoventilation, hypercapnia and hypoxemia developed. The hypercapnia resulted in clouding of the sensorium and further depression of the respiratory center. Vascular changes in the lungs, presumably the consequence of chronic hypoxemia, are believed to have contributed to the pulmonary hypertension and cor pulmonale.

Acknowledgment

I am indebted to Dr. Alfred P. Fishman, Presbyterian Hospital, New York City, for valuable advice in the preparation of this report. Dr. Abner Wolf reviewed lesions from the central nervous system.

References

1. Newman, W., Feltman, J. A. and Devlin, B. Pulmonary function studies in polycythemia vera; results in five probable cases. *Am. J. Med.*, 11: 706, 1951.
2. Ratto, O., Briscoe, W. A., Morton, J. W. and Comroe, J. H., Jr. Anoxemia secondary to polycythemia and polycythemia secondary to anoxemia. *Am. J. Med.*, 19: 958, 1955.
3. Richter, T., West, J. R. and Fishman, A. P. The syndrome of alveolar hypoventilation and diminished sensitivity of the respiratory center. *New England J. Med.*, 256: 1165, 1957.
4. Pare, P. and Lowenstein, L. Polycythemia associated with disturbed function of the respiratory center. *Blood*, 11: 1077, 1956.
5. Medical Grand Rounds, Massachusetts General Hospital. Hypoventilation syndrome. *Am. Pract. & Digest Treat.*, 7: 1165, 1956.
6. Rodman, T. and Close, H. P. The primary hypoventilation syndrome. *Am. J. Med.*, 26: 808, 1959.
7. Fishman, A. P., Turino, G. M. and Bergofsky, E. H. The syndrome of alveolar hypoventilation. *Am. J. Med.*, 23: 333, 1957.
8. Efron, R. and Kent, D. C. Chronic respiratory acidosis due to brain disease; reversal of normal electroencephalographic response to hyperventilation. *Arch. Neurol. & Psychiat.*, 77: 575, 1957.
9. Garlind, T. and Linderholm, H. Hypoventilation syndrome in a case of chronic epidemic encephalitis. *Acta med. scandinav.*, 162: 333, 1958.
10. Sarnoff, S. J., Whittenberger, J. L. and Affeldt, J. E. Hypoventilation syndome in bulbar poliomyelitis. *J. A. M. A.*, 147: 30, 1951.
11. Finley, K. H. The neuro-anatomy in respiratory failure; report of 2 cases. *Arch. Neurol. & Psychiat.*, 26: 754, 1931.
12. Scharenberg, K. Pathology of poliomyelitis treated in respirators. *J. Neuropath. & Exper. Neurol.*, 14: 297, 1955.
13. Schlesinger, M. J. New radiopaque mass for vascular injection. *Lab. Invest.*, 6: 1, 1957.
14. Naeye, R. L., Arterial changes during the perinatal period. *Arch. Path.*, 71: 121, 1961.
15. Gesell, R., Bricker, J. and Magee, G. Structural and functional organization of central mechanism controlling breathing. *Am. J. Physiol.*, 117: 423, 1936.
16. Baker, A. B. Cited in Fulton, J. F. Textbook of Physiology, 16th ed., p. 823. Philadelphia, 1949. W. B. Saunders.
17. Naeye, R. L. and Bickerman, H. A. The effects of hypoxemia on the pulmonary arterial bed of humans and rats. *Fed. Proc.*, 18: 497, 1959.
18. Naeye, R. L. Hypoxemia and pulmonary hypertension: A study of the pulmonary vasculature. *Arch. Path.*, 71: 447, 1961.
19. Horner, F. A. Neurologic disorders after Asian influenza. *New England J. Med.*, 258: 983, 1958.

Manifestations of Myocardial Involvement in Acute Reactions to Penicillin*

ROBERT F. HADEN, CAPT., MC *and* PER H. LANGSJOEN, MAJ., MC
El Paso, Texas

INVOLVEMENT OF THE heart in generalized allergic reactions has been demonstrated clinically, at autopsy, and in experimental animals in many isolated cases in the past three decades.

Wadsworth and Brown[1] in 1940, and Fox and Messeloff[2] in 1942, each reported a case showing abnormal electrocardiographic changes following serum sickness due to tetanus antitoxin. In 1950 Binder et al.[3] reported three cases with transient electrocardiographic abnormalities associated with allergic reactions to penicillin. Pfister and Plice[4] in 1950, and McManus and Lawlor[5] in 1950, reported cases of myocardial infarction following severe allergic reactions. In 1952 Foster and Layman[6] reported a case with generalized urticaria and electrocardiographic changes simulating myocardial infarction. In 1950 both Felder and Felder,[7] and Lilienfield, Hockstein and Weis,[8] reported isolated cases with electrocardiographic changes compatible with myocarditis occurring during hypersensitivity reactions to penicillin. Glotzer,[9] in 1954, reported a case with electrocardiographic changes consistent with the diagnosis of pericarditis during a hypersensitivity reaction to penicillin. In 1959 Bernreiter[10] reported a case with abnormal electrocardiographic changes during anaphylactic shock. This patient, however, was in severe shock and hypoxic. Bernreiter, therefore, postulated that both anoxia and tissue sensitivity of the myocardium accounted for the abnormal electrocardiographic findings.

In 1938 Clark and Kaplan[11] reported two deaths following serum sickness due to antipneumococcal serum. Autopsies revealed an arteritis, including the coronary arteries, similar to that found in periarteritis nodosa. They also described a diffuse cellular infiltration in the kidneys, adrenals, liver, other visceral organs and, specifically the myocardium. In 1942 French and Weller[12] demonstrated similar tissue and vascular changes in human subjects and in animals following fatal hypersensitivity reactions to sulfonamide drugs. In 1952 Waugh[13] reported a fatal anaphylactic reaction to penicillin. Acute and subacute arteritis involving the heart and other organs were found at autopsy.

Wilcox and Andrus[14] demonstrated in 1938 that isolated guinea pig hearts sensitized to horse serum would react to small amounts of antigen with tachycardia, decreased coronary blood flow and electrocardiographic abnormalities. Later, Rich and Gregory[15–18] were able to produce tissue changes in many organs of the rabbit, especially the heart, by producing anaphylactic hypersensitivity reactions. These changes showed the basic characteristics of those noted in the rheumatic conditions such as lupus erythematosus, periarteritis nodosa and rheumatic fever. Mikulicich,[19] in 1951, demonstrated abnormal electrocardiographic changes consistently in rabbits during anaphylactic reactions. In 1951 Crawford and Nassim[20] demonstrated changes in the myocardium and coronary arteries in rabbits which were similar to those noted in periarteritis nodosa and other collagen diseases following hypersensitivity reactions to horse serum.

In this article we report three cases of young men with transient abnormal electrocardiographic changes following hypersensitivity reactions to penicillin in which there was no definite associated hypoxia or complete loss of consciousness.

CASE REPORTS

CASE 1. This nineteen year old white man was given 600,000 units benzathine penicillin and 600,000 units procaine penicillin G for a sore throat

* From the William Beaumont General Hospital, El Paso, Texas.

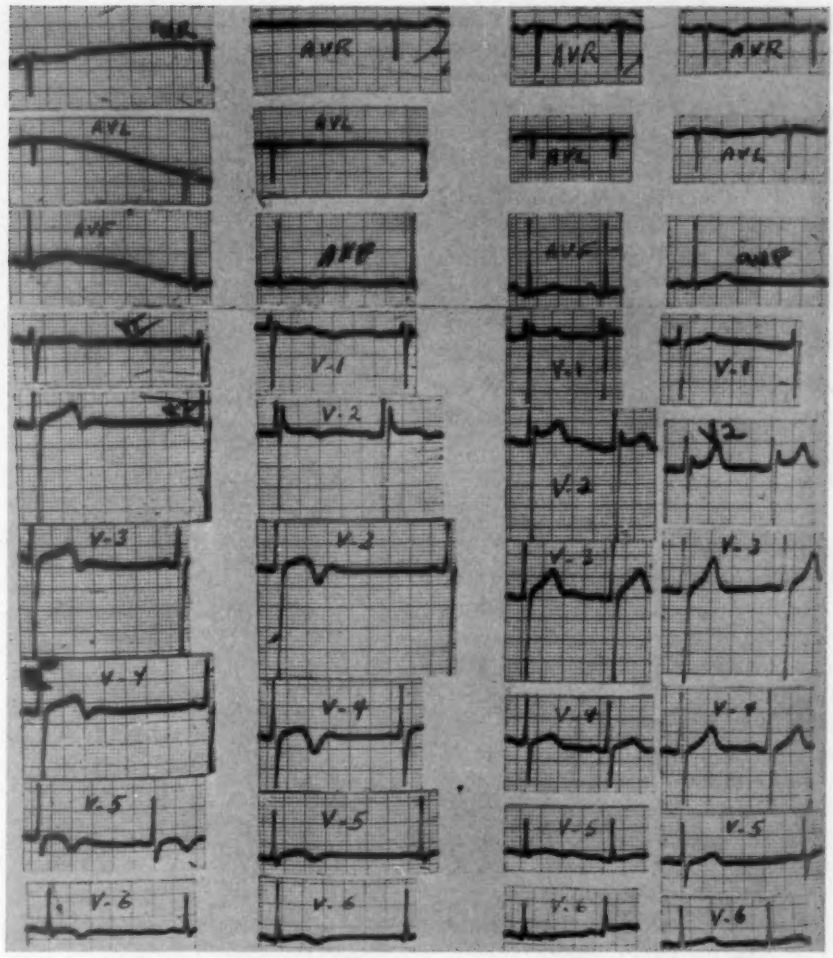


FIG. 1. Case 1. Electrocardiograms showing bradycardia and serial T wave changes following an allergic reaction to penicillin. A, September 9, 1959; B, September 11, 1959; C, September 15, 1959; D, October 29, 1959.

on the day of admission. He had no previous history of allergy to penicillin. Very shortly after injection he became weak and dizzy. He was put in bed and fifteen minutes later his blood pressure was 70 to 80/0 mm. Hg and his heart rate was 40 per minute. He was treated with diphenhydramine, 50 mg. intramuscularly and 50 mg. intravenously, 800,000 units of penicillinase intravenously, 0.5 cc. of 1:1000 epinephrine subcutaneously and oxygen by mask and was brought to this hospital.

Physical examination on admission revealed a blood pressure of 120/58 mm. Hg, a pulse rate of 88 per minute, respirations of 20 per minute. His temperature was 101°F. The patient did not appear acutely ill. The throat was inflamed. The chest was clear to auscultation and percussion. The heart was of normal size with a normal rate and rhythm. There was a grade 2, midsystolic, blowing murmur heard best at the apex and not transmitted into the axilla. He showed a definite puffiness of the face but no discrete urticarial lesions.

Laboratory Findings: An electrocardiogram shortly after admission revealed bradycardia, inverted T waves in aVF and V_2 through V_6 and an upright T wave in aVR (Fig. 1). X-ray examination of the chest was not remarkable. Throat culture showed no pathogens. A white blood cell count revealed 12,000 cells with 90 per cent neutrophils, 6 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophils. The sedimentation rate was 23 mm. per hour. The hematocrit was 42 per cent. The cardiolipin microflocculation test for syphilis was negative. The urinalysis was negative.

Subsequent Course and Treatment: Shortly after admission, a bradycardia of 36 per minute developed again and the patient required sublingual isoproterenol to maintain his pulse rate above 40 per minute. After ten days of hospitaliation he was able to maintain a pulse of between 50 and 60 per minute with no stimulation. He was also treated with forty units of ACTH in 1,000 cc. of 5 per cent glucose in water daily for two days. He was then given 60 mg. of prednisone daily by mouth. This was gradually tapered and discontinued three weeks later. He

remained weak and dizzy on arising for the first five days of his hospitalization and was kept at bed rest. After five days he had dizziness only on stooping or suddenly assuming the erect position. After the tenth hospital day he remained asymptomatic.

On the eleventh hospital day the patient's electrocardiogram was unremarkable with the exception of an inverted T wave in aVF. A follow-up electrocardiogram taken four weeks later was within normal limits (Fig. 1). He was discharged three weeks after admission and was asymptomatic six weeks after admission with a normal electrocardiogram.

Comment: The syncopal episodes, bradycardia and electrocardiographic abnormalities were thought to be due to a hypersensitivity reaction to penicillin.

CASE 2. This twenty-three year old white man was well until four days prior to admission when a swollen, reddened right knee developed. Of significance also was a history of his having had a white urethral discharge associated with dysuria one week prior to admission which cleared spontaneously two days prior to admission.

On the day of admission he was given an injection of 600,000 units procaine penicillin. Several minutes after the injection he became faint but did not lose consciousness. Generalized urticaria, severe itching, increased lacrimation and swelling of the tongue developed. He was given 50 mg. of diphenhydramine intramuscularly and transferred to this hospital.

Physical examination on admission revealed a pulse of 104, respirations of 20 per minute, a blood pressure of 130/60 mm. Hg, and a temperature of 101.6°F. He was moderately uncomfortable because of the pruritus. There was a generalized urticaria, a swollen, red, warm, painful right knee and swelling of the tongue. The eyes were injected and showed increased lacrimation.

Laboratory Findings: An electrocardiogram on admission revealed slightly inverted T waves in leads aVF and V_3 through V_6 (Fig. 2). X-ray examination of the chest was not remarkable Urinalysis was within normal limits. White blood cell count revealed 9,100 cells with 71 per cent neutrophils, 24 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. Hemoglobin was 15.3 gm. and sedimentation rate was 34 mm. per hour. The latter was 12 mm. per hour on the eighth hospital day. The latex agglutination test was nonreactive. Lupus erythematosus preparations were negative for lupus erythematosus cells on three successive days. An antistreptolysin O titer was less than 50 units and a test for C-reactive protein was negative. A cardiolipin microflocculation test for syphilis showed no reaction.

Subsequent Course: The patient was treated with bed rest, diphenhydramine, ephedrine and salicylates. He became asymptomatic after the fourth hospital day. The right knee returned to normal size, color and temperature and was no longer painful. The electrocardiographic changes gradually improved and on the ninth hospital day the record was within normal limits (Fig. 2). He remained asymptomatic and his electrocardiograms remained within normal limits. He was discharged two weeks after admission.

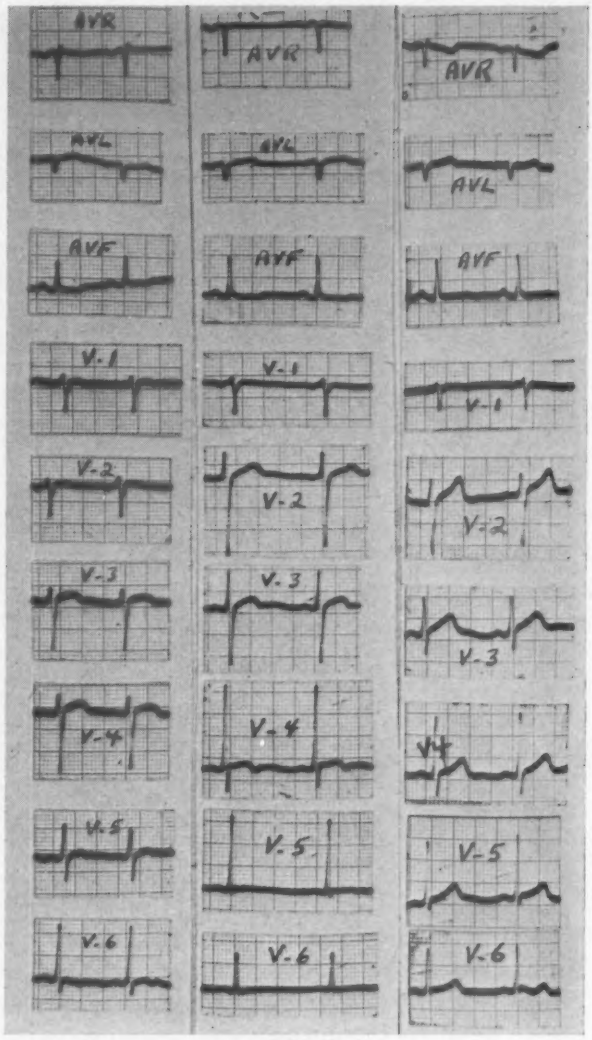


FIG. 2. Case 2. Electrocardiograms showing serial T wave changes following an allergic reaction to penicillin. A, September 27, 1959; B, September 28, 1959; C, October 2, 1959.

Comment: Reiter's syndrome was considered the most likely explanation of his initial joint, conjunctival and urethral abnormalities. The urticaria, syncopal episode and electrocardiographic abnormalities were thought to be due to an allergic reaction to penicillin.

CASE 3. This thirty year old white man was well until one month prior to admission when right otitis media and pharyngitis developed. He was treated initially with oxytetracycline with no improvement

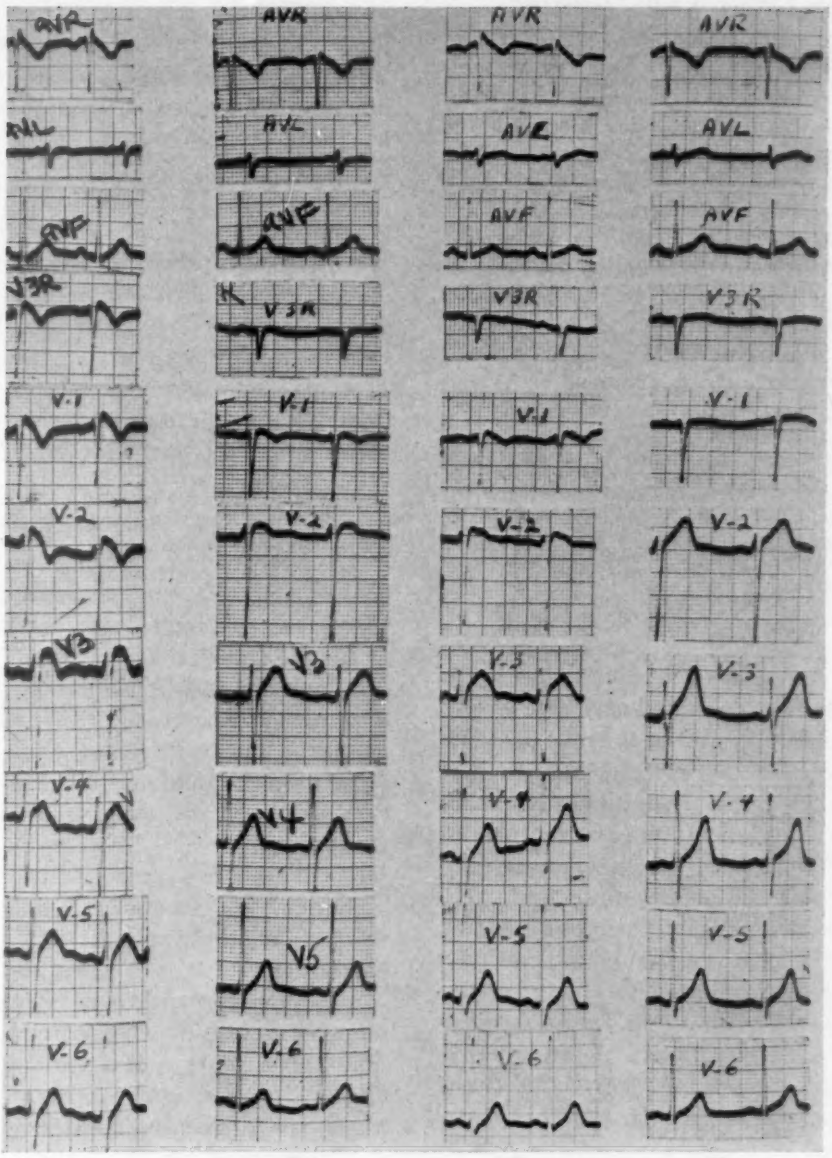


FIG. 3. Case 3. Electrocardiograms showing serial S-T and T wave changes following an allergic reaction to penicillin. A, May 17, 1960; B, May 18, 1960; C, May 19, 1960; D, May 20, 1960.

and three weeks prior to admission was given daily injections of penicillin and streptomycin which were continued for one week. Five days prior to admission generalized urticaria developed followed by migratory arthralgia involving the wrists, shoulders, elbows and knees. He had a low grade fever. Two days prior to admission the rash became more severe, involving the palms of the hands and soles of the feet, and he was admitted to this hospital.

Physical examination on admission revealed a temperature of 103°F., pulse of 120 per minute, blood pressure of 120/80 mm. Hg and respirations of 16 per minute. The patient appeared ill. There was a perforation in the right tympanic membrane with a purulent discharge. The pharynx was normal. There was a generalized giant urticarial rash over the entire body including the palms of the hands and soles of the feet. These lesions were noted over various joints which caused some discomfort on manipulation of the joint, but there was no joint swelling or intrinsic pain involving any joint.

Laboratory Findings: An electrocardiogram on admission revealed elevation of S-T segments and inversion of T waves in V_1 and V_2 with a diphasic T wave in V_3. Electrocardiograms on the following two days were within normal limits with the exception of a diphasic T wave in V_2. Subsequent electrocardiograms were not remarkable (Fig. 3). A cardiolipin microflocculation test for syphilis was negative. Urinalysis was within normal limits. The white

blood count revealed 7,800 cells with 74 per cent neutrophils, 25 per cent lymphocytes and 1 per cent monocytes. Hemoglobin was 14.1 gm. and hematocrit 44 per cent. A blood culture showed no growth. Sedimentation rate was 32 mm. per hour. Three lupus erythematosus preparations were negative for lupus erythematosus cells on successive days. The latex agglutination test was nonreactive. An antistreptolysin O titer was 100 units and was unchanged one week later. Chest x-ray examination was normal.

The patient was treated with bed rest, diphenhydramine, tripelennamine and salicylates. On this regimen his fever disappeared and the urticaria subsided over the next three days. Thereafter, he was asymptomatic.

Comment: This case was thought to represent a generalized urticarial reaction to penicillin with suggestive evidence of allergic myocarditis, both of which cleared promptly with antihistamine therapy.

Comment

These three young men with transient abnormal electrocardiographic changes give strong support to the presumption that the myocardium and possibly the coronary arteries occasionally are involved in allergic reactions. None of these men had a reaction which would clinically be called severe, yet they all showed definite electrocardiographic abnormalities and one showed impairment of circulation as manifested by marked bradycardia which necessitated the use of isoproterenol for the first ten days of his hospitalization. It would appear that the heart may participate in an allergic tissue reaction to a variable degree, at times simulating myocarditis, pericarditis or myocardial infarction.

Arteritis in allergic reactions has been reported by several authors both experimentally in animals and in autopsied human cases. This has been likened histologically to the arteritis found in periarteritis nodosa and other collagen diseases. Myocardial infarction has been reported following allergic reactions presumptively due to this arteritis, yet the importance of circulatory collapse in precipitating myocardial ischemia cannot be excluded. It is, therefore, well to consider the possibility of myocardial involvement in any allergic reaction and especially those with associated syncopal episodes, bradycardia or generalized urticaria. Acute arteritis or tissue reaction in the myocardium may explain some of the cases of sudden death in allergic reactions.

The electrocardiographic abnormalities seen in our three cases and others reported in the literature are rapidly apparent and usually transient. This sudden onset with prompt remission is in accord with acute allergic reactions as manifested in other tissues, most obviously the skin.

Criep,[21] in 1931, studied the electrocardiographic changes in allergic reactions in animals. He postulated that these disturbances in the cardiac mechanism were due to anoxia. There was no evident anoxia in our three cases. Although anoxia can cause these changes, and perhaps sometimes does, there may also be a tissue reaction in the myocardium and coronary arteries in response to the specific antigen in many cases.

Summary

1. Myocardial damage as evidenced by electrocardiographic changes is reported in three cases of allergic reactions to penicillin.

2. Myocardial involvement following allergic reactions has been previously demonstrated clinically, experimentally and on necropsy studies. The pathologic changes consisted of edema and cellular infiltration in the myocardium, and an arteritis of the coronary arteries.

3. The importance of myocardial anoxia secondary to circulatory collapse in the production of these changes has not been well established.

4. Our cases showed electrocardiographic changes in the absence of circulatory collapse. The rapid onset and transient nature of these changes is similar to allergic reactions in other, more easily observed, tissues.

5. Syncope or bradycardia in allergic reactions may be evidence of myocardial involvement and justifies electrocardiographic studies.

References

1. Wadsworth, G. H. and Brown, C. H. Serum reaction complicated by acute carditis. *J. Pediatrics*, 17: 801, 1940.
2. Fox, T. and Messeloff, C. R. Electrocardiographic changes in case of serum sickness due to tetanus antitoxin. *New York J. Med.*, 42: 152, 1942.
3. Binder, M. J., Gunderson, H. J., Cannon, J. and Rosove, L. Electrocardiographic changes associated with allergic reactions to penicillin. *Am. Heart J.*, 40: 940, 1950.
4. Pfister, C. W. and Plice, S. G. Acute myocardial infarction during a prolonged allergy reaction to penicillin. *Am. Heart J.*, 40: 945, 1950.
5. McManus, J. F. and Lawlor, J. J. Myocardial infarction following administration of tetanus antitoxin. *New England J. Med.*, 242: 17, 1950.

6. Foster, R. F. and Layman, J. D. Generalized urticaria with electrocardiographic changes simulating myocardial infarction. *J. A. M. A.*, 148: 203, 1952.
7. Felder, S. L. and Felder, L. Unusual reactions to penicillin. *J. A. M. A.*, 143: 361, 1950.
8. Lilienfeld, A., Hochstein, E. and Weiss, W. Acute myocarditis with bundle branch block due to sulfonamide sensitivity. *Circulation*, 1: 1060, 1950.
9. Glotzer, S. L. Electrocardiographic changes during sensitivity reaction to penicillin. *Am. Heart J.*, 47: 3000, 1954.
10. Bernreiter, M. Electrocardiogram of patient in anaphylactic shock. *J. A. M. A.*, 170: 1628, 1959.
11. Clark, E. and Kaplan, B. K. Endocardial arterial and other mesenchymal alterations associated with serum disease in man. *Arch. Path.*, 24: 458, 1937.
12. French, A. J. and Weller, C. V. Interstitial myocarditis following clinical and experimental use of sulfonamide drugs. *Am. J. Path.*, 18: 109, 1942.
13. Waugh, D. Myocarditis, arteritis and focal hepatic, splenic, and renal granuloma apparently due to penicillin sensitivity. *Am. J. Path.*, 28: 437, 1952.
14. Wilcox, H. B. and Andrus, E. C. Anaphylaxis in isolated heart. *J. Exper. Med.*, 57: 169, 1938.
15. Rich, A. R. and Gregory, J. E. Experimental evidence that lesions with basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. *Bull. Johns Hopkins Hosp.*, 73: 239, 1943.
16. Rich, A. R. and Gregory, J. E. On anaphylactic nature of rheumatic pneumonitis. *Bull. Johns Hopkins Hosp.*, 74: 465, 1943.
17. Rich, A. R. and Gregory, J. E. Further experimental cardiac lesions of rheumatic type produced by anaphylactic hypersensitivity. *Bull. Johns Hopkins Hosp.*, 75: 115, 1944.
18. Rich, A. R. and Gregory, J. E. Experimental anaphylactic lesions of the coronary arteries of "sclerotic" type, commonly associated with rheumatic fever and disseminated lupus erythematosus. *Bull. Johns Hopkins Hosp.*, 81: 313, 1947.
19. Mikulicich, G. Electrocardiographic changes in experimental anaphylactic reactions. *J. Allergy*, 22: 249, 1951.
20. Crawford, T. and Nassim, J. R. Cardiac lesions in rabbits following injections of horse serum. *J. Path & Bact.*, 63: 619, 1951.
21. Criep, L. H. Electrocardiographic studies of effect of anaphylaxis on cardiac mechanism. *Arch. Int. Med.*, 48: 19, 1098, 1931.

Successful Removal of a Pheochromocytoma Four Weeks after Acute Myocardial Infarction*

PAUL E. MATTMAN, M.D.

Detroit, Michigan

ALTHOUGH the coexistence of pheochromocytoma and myocardial infarction seems well recognized, the actual incidence of coronary thrombosis in this disease is not known and actual individual case reports, describing the concurrence of these two clinical entities, have appeared only infrequently.[1–3] Reports have appeared about the effects of catecholamines and, more specifically, pheochromocytoma on the electrocardiogram in humans[4–6] and the deleterious effects of these adrenalin-like substances on the myocardium in the rabbit have been carefully documented[7] but actual case reports of coronary thrombosis in patients with pheochromocytoma are infrequent.

The following case is reported because myocardial infarction developed relatively silently in a patient with classical clinical manifestations of pheochromocytoma. Of further interest is the successful removal of the tumor with apparently complete subsequent cure, despite the recent myocardial infarction.

CASE REPORT

A forty-five year old Polish factory worker was admitted to the Medical Service because of an acute episode of hypertension following the intravenous administration of aminophylline by his physician. The patient on admission gave a six month history of attacks of throbbing chest pain and headache, with occasional associated vomiting, lasting from several minutes to several hours. Wide fluctuations in blood pressure had been noted by his attending physician. These did not respond well to reserpine, 0.25 mg. twice daily.

On admission, this stockily built, perspiring white male complained of recurrent attacks of transient chest pain and headaches. His blood pressure was 190/100 mm. Hg in the right arm. The ocular fundi showed grade 1 hypertensive retinopathy. The lungs were clear to percussion and auscultation. The heart was not enlarged. The rhythm was regular and the rate was 110/minute. There were no murmurs, gallop or duplications. The abdomen was normal. Massage of both sides of the abdomen did not result in elevation of systolic blood pressure. Genitalia were normal; peripheral pulses were readily felt; the skin revealed nothing abnormal and there were no neurofibromas.

The patient was considered to have hypertensive cardiovascular disease and he was treated with bed rest, low salt diet, chlorothiazide (500 mg. twice daily) and reserpine (0.25 mg. twice daily). Because, however, of continued episodes of sweating, vomiting and chest pain, and because of fluctuations of blood pressure, an additional diagnosis of pheochromocytoma was considered. Postural hypotension was noted on the third admission day with supine blood pressure of 160/80 mm. Hg and a standing blood pressure of 60/40 mm. Hg. Urinary catecholamines were obtained at this point. It was decided not to resort to Regitine,® benzodioxane or histamine tests because of electrocardiographic evidence of myocardial infarction, appearing during the early days of hospitalization, as described later.

Electrocardiograms: On the day of admission (August 12, 1958), the electrocardiogram revealed small Q waves and slightly elevated S-T segments in leads II, III and aVF, together with peaked T waves in V_1 to V_4, suggesting possible early acute posterior myocardial infarction (Fig. 1). There was high A-V nodal rhythm, converting to sinus rhythm in V_4. A repeat electrocardiogram on August 14, 1958 (Fig. 1) showed deep Q waves and inverted T waves in leads II, III and aVF, as well as T wave inversions in V_5 and V_6. These findings indicated a massive posterior myocardial infarction with anterolateral extension. They were unexpected, inasmuch as precordial pain was never sustained for more than a few minutes at a time. The patient was treated with anticoagulants (dicoumarol), with prothrombin times maintained at approximately twice control values. Serial electrocardiograms revealed normal evolution of the myocardial infarction (Fig. 1).

* From the Department of Internal Medicine, St. Francis Hospital and Wayne State University, Detroit, Michigan.

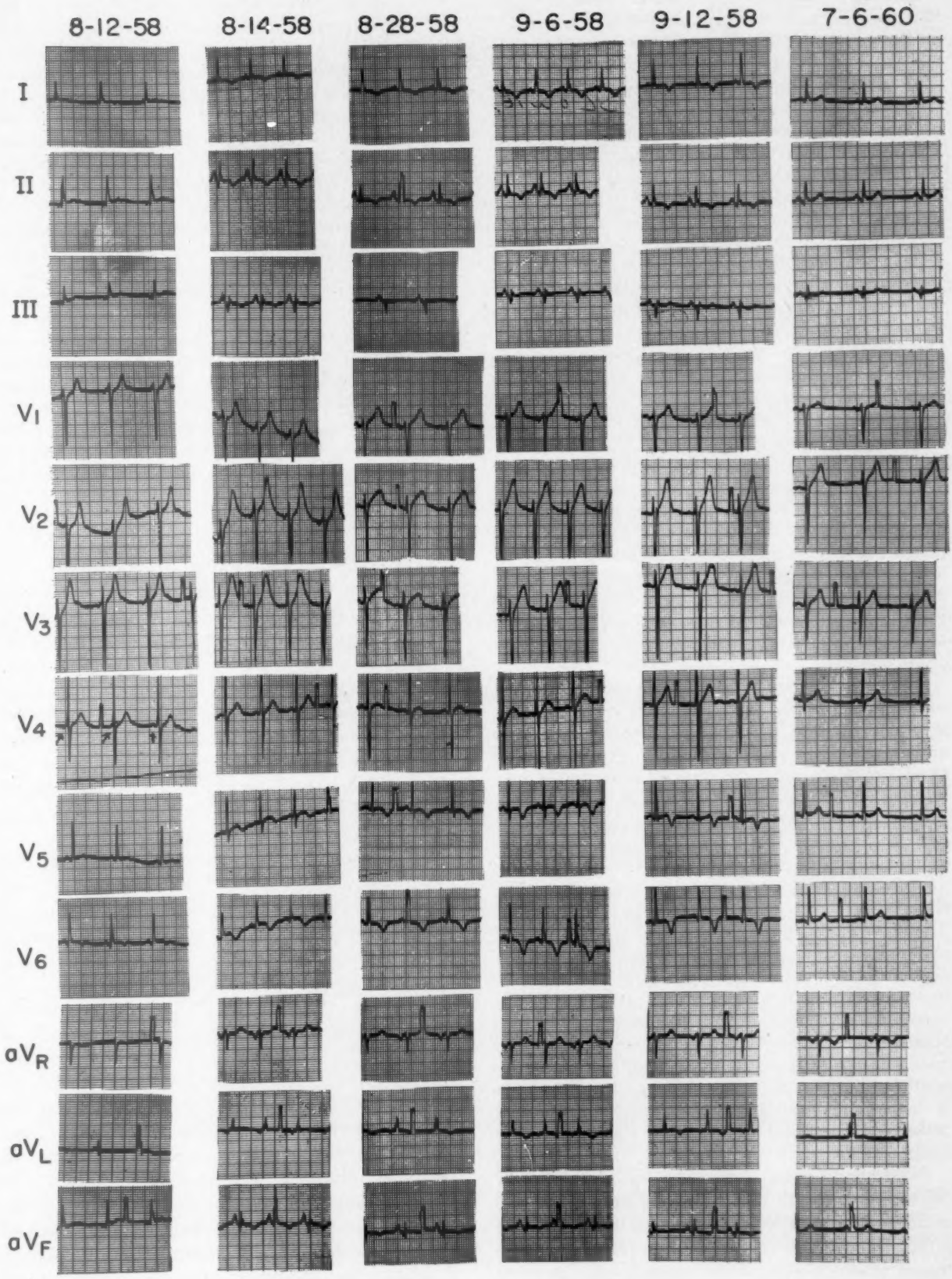


FIG. 1. Serial electrocardiograms showing evolution of a recent posterior myocardial infarction.

Laboratory Findings: Serum transaminase (S-GOT) titers were 28 units on August 14, 44 on August 20, 99 on September 9, 79 on September 14 (the latter two values being postoperative). Urinary catecholamines, as obtained on August 15, 1958, were 386 μg./100 cc. (normal, 0–14), thus lending support to the diagnosis of pheochromocytoma. A fasting blood sugar was 159 mg./100 cc., also supporting the diagnosis of pheochromocytoma. A basal metabolic rate on September 3, 1958 was plus 38 per cent. Protein bound iodine on August 16, 1958, was 4 μg./100 cc., eliminating hyperthyroidism as the cause of the evident hypermetabolism.

Intravenous pyelograms on August 20, 1958 revealed an apparent soft tissue density of circumscribed character, superimposed on the upper pole of the right kidney. Retrograde pyelography showed similar findings. Presacral air insufflation on August 20, 1958 was unsatisfactory.

Surgical Findings and Operative Course: On August 20, 1958 Regitine was given by mouth (50 mg. four times daily) to help level the patient's hypertensive peaks. The decision to remove this tumor was made as soon as his cardiac status would permit, to prevent further damage to his myocardium by fluctuations in blood pressure and by excessive circulating catecholamines. The retroperitoneal route was elected because the tumor had been reasonably well localized by roentgenography and because it was believed that this approach involves less trauma and less manipulation of the tumor.

Accordingly, after twenty-six days of therapy for myocardial infarction, a large globular tumor, measuring 10 cm. in its greatest diameter, was removed under gas-oxygen-ether by the retroperitoneal route. Despite continued anticoagulation (prothrombin time on day of operation was twenty-two seconds with control sixteen seconds), bleeding was minimal. Systolic blood pressure reached 210 mm. Hg during manipulation, dropping to 60 mm. Hg systolic as soon as blood supply to the tumor was severed and clamped.

Following this operation arterial pressure had to be maintained with continuous intravenous norepinephrine (4 to 8 cc. per 1,000 cc. of 5 per cent glucose in water infused at varying rates, according to the needs of the patient), administered over a period of approximately sixty hours. The patient remained essentially asymptomatic, without any further precordial pain, headaches or vomiting. After cessation of the norepinephrine, his arterial pressures remained between 120/80 and 150/90 mm. Hg without any further medication.

Postoperative Course: Following discharge, after a suitable three month rest period, the patient returned to his work, performing heavy labor during at least a forty hour week. There were no further recurrences of headaches, sweating, precordial pain or weakness. During a recent examination on July 5, 1960 he appeared well. The cardiovascular system was normal. Blood pressure was 120/70 mm. Hg. The electrocardiogram showed almost complete return to normal, with small Q waves in leads III and aVF being the only remnants of the former infarction (Fig. 1). Urinary catecholamines were 16 μg./100 cc., thus indicating excellent recovery and fairly well excluding the possibilities of either malignant degeneration of the tumor or multiple tumors.

Pathologic Report: The ovoid tumor measured 12 cm. in diameter and weighed 254 gm. (Fig. 2). Its external surface was smooth, irregular, congested, and its cut surface showed some marbling with gray, bluish and yellow areas of coloration being noted on a dark brown background. Microscopic sections (Fig. 2B) showed an encapsulated benign new growth, consisting of a syncytium of angular and polyhedral cells of uniform size and shape, staining uniformly with eosin and hematoxylin. The nuclei were small, round and stained uniformly. Another section revealed adrenal cortex with compression atrophy and degeneration of all zones. There was no evidence of malignancy. *Microscopic diagnosis:* pheochromocytoma.

Comments

The clinical findings in this patient were classical for pheochromocytoma, as manifested by fluctuating hypertension, marked postural hypotension, attacks of palpitation with headache and precordial pain. Elevated basal metabolic rate in the presence of a normal protein bound iodine and hyperglycemia were also classical manifestations of this syndrome. Elevation of urinary catecholamines beyond that expected from myocardial infarction alone[8] established the diagnosis and intravenous pyelography localized the tumor.

The unusual and remarkable feature of this case was the unexpected electrocardiographic evidence of acute posterior myocardial infarction developing in the absence of classical clinical manifestations of coronary thrombosis, such as sustained precordial pain, leukocytosis and fever. The lack of elevation of serum glutamic oxalacetic transaminase prior to operation was also atypical, in view of the massive extent of this infarction, as revealed by electrocardiography. These electrocardiographic changes were unmistakable and were clearly far more extensive than the transient ischemic changes described elsewhere[4–6] in cases of catecholamine excreting adrenal tumors. The mechanism of the production of this myocardial infarction is probably the abrupt reduction in circulation in a previously atherosclerotic coronary vessel during repeated bouts of postural hypotension, with the toxic effects of

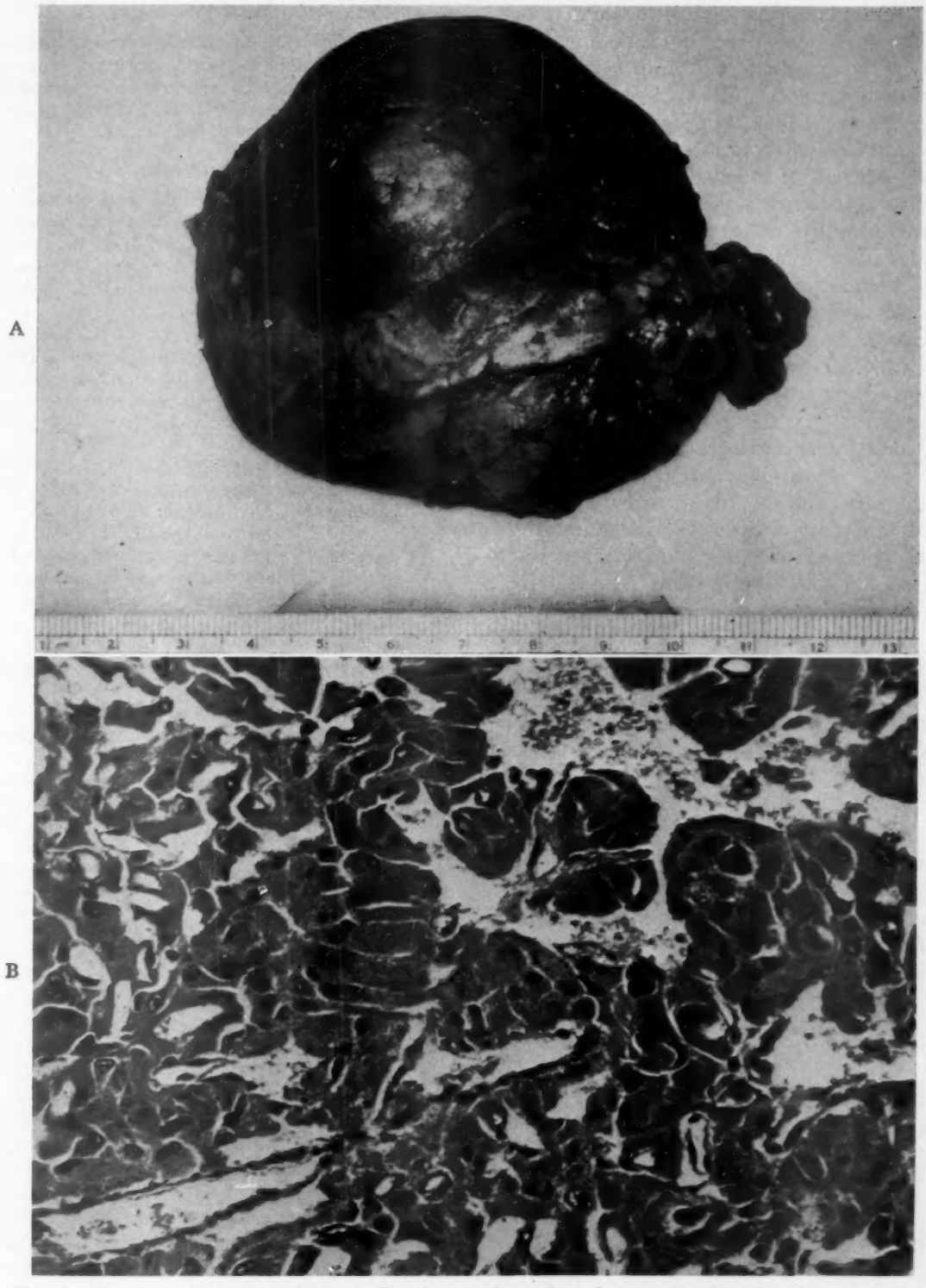


FIG. 2. A, gross appearance of tumor; B, microscopic section of tumor showing pheochromocytoma.

norepinephrine on the myocardium, as described elsewhere,[7] contributing to this damage.

The timing of the removal of this pheochromocytoma presented a problem. Operative intervention before adequate scar tissue formation of the myocardium could be fatal. Prolonged procrastination, on the other hand, could expose the patient to further damage of his myocardium from the effects of fluctuating blood pressure and excess circulating catecholamines. A compromise time of four weeks after the onset of myocardial infarction was

chosen, keeping in mind, however, high mortality described elsewhere in this operation (as high as 25 per cent),[9,10] even in the absence of complicating myocardial infarction.

The posterior surgical approach was elected to reduce manipulation of the tumor to a minimum, at the risk of missing multiple tumors. Removal of this tumor was not associated with significant bleeding, despite continued anticoagulation, nor was it associated with catastrophic fluctuations in the blood pressure, because of administration of Regitine preoperatively and norepinephrine postoperatively. Postoperative electrocardiograms showed normal evolution of the patient's infarction and the postoperative elevations of serum transaminase titers were thought to reflect operative skeletal muscle damage rather than myocardial necrosis. The continued elevation of his urinary catecholamines five days postoperatively at first suggested aberrant tumors or a metastasizing one, but his subsequent course, with complete recovery, together with the absence of hypertension at the present time and normal urinary catecholamines, rule out this possibility. In retrospect, the sustained elevation may simply have been due to continued intravenous administration of norepinephrine postoperatively.

Summary

A patient with clinical features of pheochromocytoma has been presented because of the successful removal of the tumor four weeks after an acute myocardial infarction. Two years after this operation the patient is entirely well and his blood pressure and urinary catecholamines are normal.

Acknowledgment

I am grateful to Dr. Richard J. Bing, Chairman of the Department of Medicine, for reviewing this paper; to Dr. Raymond Kokowicz for interpreting electrocardiograms; and to Dr. Alexander Pietra for his assistance in the clinical management of the patient.

References

1. Boldt, M. H., Flexner, M. and Ortner, A. B. Pheochromocytoma associated with painless myocardial infarction. *Ann. Int. Med.*, 46: 1165, 1957.
2. Priest, W. M. Pheochromocytoma with fatal myocardial infarction in a man aged 22. *Brit. M. J.*, 2: 860, 1952.
3. Wilkins, R. W., Greer, W. E. R., Culbertson, J. W., Halperin, M. H., Litter, J., Burnett, C. H. and Smithwick, R. H. Extensive laboratory studies of a patient with pheochromocytoma before and after successful operation. *Arch. Int. Med.*, 86: 51, 1950.
4. Sayer, W. J., Moser, M. and Mattingly, T. W. Pheochromocytoma and the abnormal electrocardiogram. *Am. Heart J.*, 48: 1, 1954.
5. Cannon, P. and Sjostrand, T. Electrocardiographic changes seen in cases of pheochromocytoma compared with changes experimentally evoked by adrenaline. *Scandinav. J. Clin.& Lab. Invest.*, 4: 266, 1952.
6. Cannon, P. J. Some newer aspects of electrocardiography: a study of 16 cases of pheochromocytoma. *Irish J. M. Sc.*, 6: 359, 1954.
7. Raab, W. Key position of catecholamines in functional and degenerative cardiovascular pathology. *Am. J. Cardiol.*, 5: 571, 1960.
8. Richardson, J. A., Woods, E. F. and Bagwell, E. E. Circulating epinephrine and norepinephrine in coronary occlusion. *Am. J. Cardiol*, 5: 613, 1960.
9. Labbé, M., Tinel, J. and Doumer, E. Crises solaries et hypertension paroxystique en rapport avec une tumeur surrénale. *Bull. et mém. Soc. méd. hôp. Paris*, 46: 982, 1922.
10. Graham, J. B. Pheochromocytoma in hypertension; an analysis of 207 cases. *Internat. Abst Surg.*, 92: 105. 1951.

Wolff-Parkinson-White Syndrome Associated with Thyrotoxicosis*

LALBHAI M. SANGHVI, M.R.C.P. (London) *and* KUSHAL BANERJEE, M.D.

Jaipur, India

IN THYROTOXICOSIS cardiac arrhythmias other than atrial fibrillation are rare. Atrial flutter, paroxysmal tachycardias of various types and heart block have seldom been reported. Unlike fibrillation, these arrhythmias are not influenced by thyroidectomy and their direct causal connection with overactive thyroid remains in doubt.[1] Occurrence of Wolff-Parkinson-White (WPW) syndrome in association with thyrotoxicosis has been reported.[2–4] Hyperthyroidism was noted in 6 per cent of the cases of WPW syndrome, but actually seems to be more common than that figure would indicate.[2] The WPW beats usually disappeared after thyroidectomy, suggesting that there may be some specific causal relationship between the WPW syndrome and hyperthyroidism. The purpose of this paper is to report a case of WPW syndrome associated with thyrotoxicosis, which may help in the understanding of the mechanism of WPW syndrome.

CASE REPORT

A forty year old housewife was admitted to the hospital on December 1, 1958, with the complaints of exertional dyspnea for the past year and dry cough for the preceding fifteen days. The dyspnea had increased during the past two months and at the time of admission it would appear on walking a few steps. She denied any history of pain in the chest, attacks of tachycardia, palpitation or diarrhea.

On examination the pulse was 130 per minute and the blood pressure 110/65 mm. Hg. There was no enlargement of the thyroid gland, and no tremors or exophthalmos could be detected. Roentgenologic examination showed a normal-sized heart. An electrocardiogram (Fig. 1A) showed a bigeminal rhythm with alternate WPW complexes, S-T segment depression in both types of complexes in the limb leads and lateral precordial leads, and a rate of 130 per minute. Several long records were obtained but a transient change to normal conduction was observed only once (Fig. 1B). Effects of carotid sinus pressure and of exercise are illustrated in Figure 2.

The history and the electrocardiogram were suggestive of coronary artery disease with cardiac failure. The patient was given digoxin from December 5, with a gradual decrease of heart rate. Daily electrocardiograms continued to show alternate WPW complexes for the next two weeks except for transient changes on two occasions. On December 15 normal conduction in successive beats was seen (Fig. 3A), and on December 17 successive WPW beats were seen up to lead aVL with change to alternate WPW beats again from lead aVF (Fig. 4). From December 19 on the tracings showed normal type of conduction in all the beats. On December 27 the heart rate had decreased to 88 per minute (Fig. 3B) and the patient otherwise felt well and was discharged from the hospital with instructions to continue taking one tablet (0.25 mg.) of digoxin daily. Subsequent tracings taken in the month of January 1959 continued to show normal type of conduction in all beats.

The patient was not seen until April 24, 1959, when she was readmitted with the complaint of swelling of the neck for the past month. She had continued to take digoxin and there was no dyspnea. On examination the blood pressure was 130/62. There was now definite slight diffuse enlargement of the thyroid gland, fine tremors of the fingers and slight exophthalmos. The electrocardiogram showed normal type of QRS complexes (Fig. 5A) with a rate of 98 per minute. Exercise and carotid sinus pressure produced no other effect except slight acceleration or slowing, respectively, of the heart rate. The basal metabolic rate was plus 42 per cent. The diagnosis of thyrotoxicosis was now made and digoxin was discontinued. On May 1 the electrocardiogram showed increased heart rate of 122 per minute with reappearance of alternate WPW beats. The patient was now given methylthiouracil, 300 mg. daily. QRS complexes, all of normal type, were recorded on May 13 when the heart rate was 100 per minute, and subsequently. On July 26 the heart rate decreased to 78 to 83 per minute and there were no manifestations of hyperthyroidism. The electro-

* From the Department of Cardiology, Sawai Man Singh Hospital and Medical College, Jaipur, India.

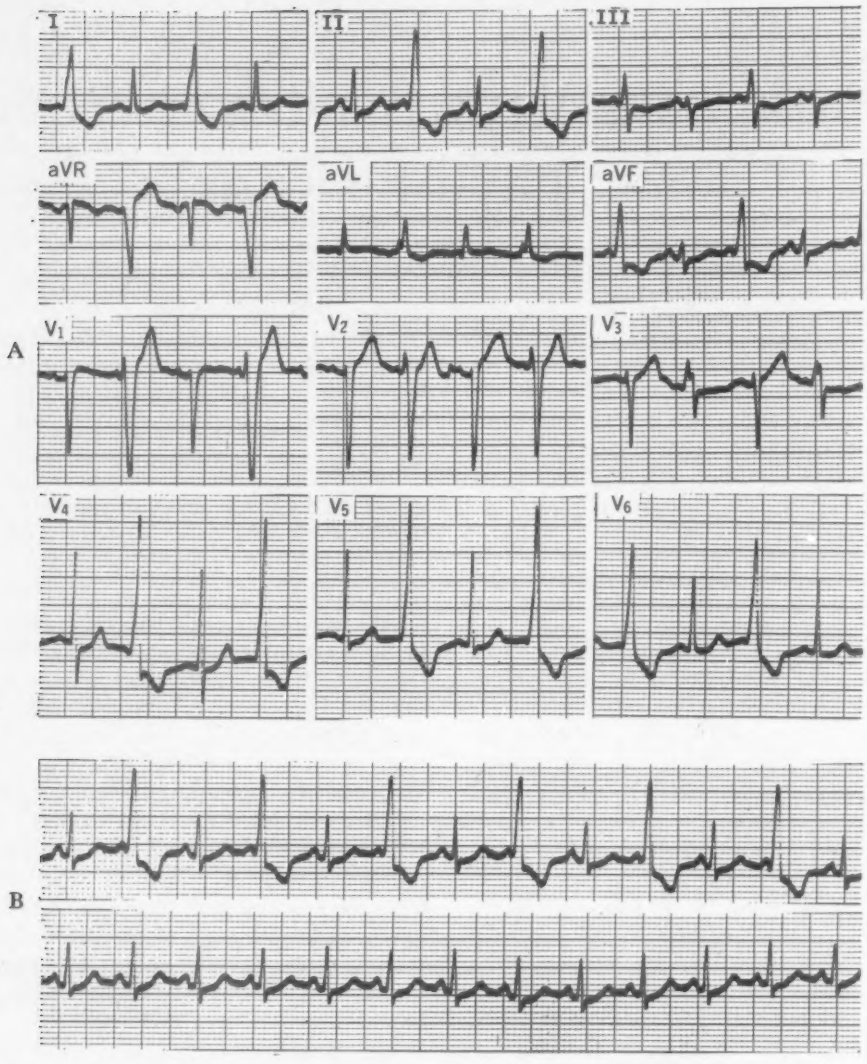


FIG. 1. Electrocardiograms on admission. A, QRS complexes of normal duration (0.06 second) with a P-R interval of 0.12 second alternating with aberrant QRS complexes with prolonged duration of 0.10 second occurring with a shorter P-R interval of 0.08 second. Typical slurring of the initial component (delta wave) in the aberrant QRS in lead I and constant P-R interval in these aberrant beats suggest presence of WPW type of conduction in these beats. The heart rate is 130 per minute. There is S-T segment depression in both type of complexes in the limb leads and lateral precordial leads. B, strips of lead II. The lower strip shows spontaneous change to normal conduction in all the beats without any change of heart rate.

cardiogram showed slight S-T segment and T wave changes (Fig. 5B). A single two-step exercise test was now negative.

COMMENT

This case presents several interesting features. Occurrence of successive WPW beats consistent with the diagnosis of WPW syndrome[5,6] was seen only on two occasions, and in those, transiently; once after exercise and once during the administration of digitalis. The WPW beats in other records alternated with normally conducted beats. Occurrence of alternate WPW beats has been reported in several instances. The present case, however, showed this type of bigeminy persistently until the WPW beats disappeared following administration of digitalis or methylthiouracil during the first and second periods of observation, respectively. There was transient change to normal conduction on only two occasions. WPW conduction in alternate beats has been suggested to be due to fluctuating vagal tone.[7] Such an explanation does not seem plausible because it is most un-

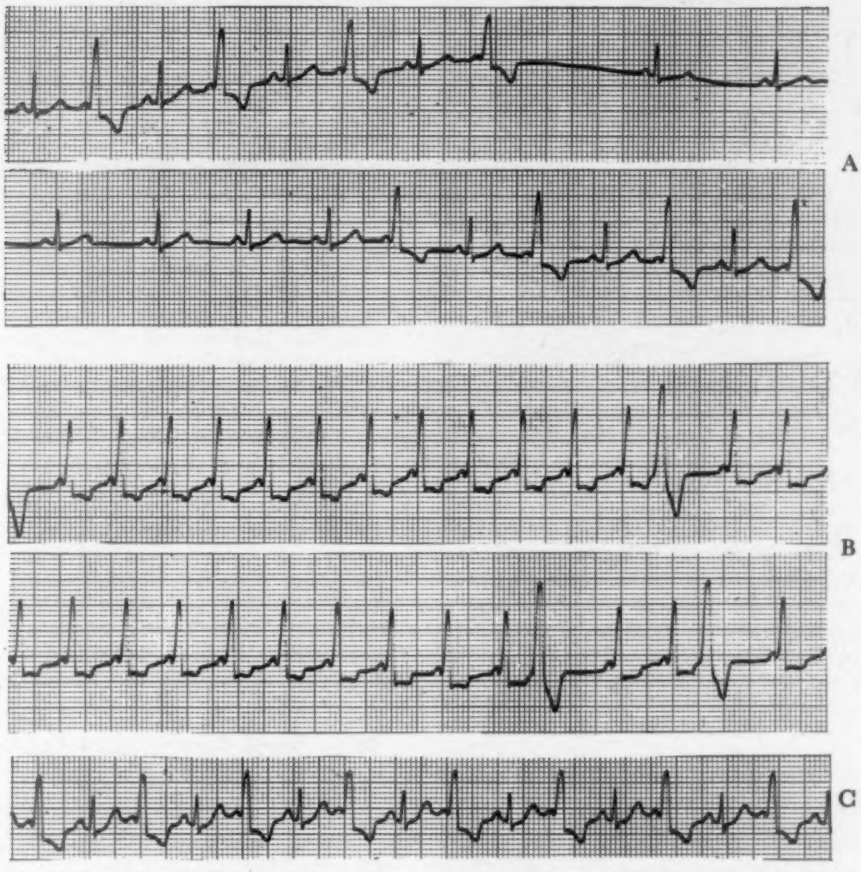


FIG. 2. Electrocardiograms obtained on December 2 (lead II). A, effect of carotid sinus pressure. The two strips are continuous. Soon after application of pressure there occurs a pause of 1.32 seconds after the last WPW beat which is terminated by a normally conducted beat. After release of pressure the sinus rate speeds up with reappearance of alternate WPW beats. B, effect of one-half Master's exercise test. The two stips are continuous. The record shows acceleration of heart rate to 156 per minute, successive QRS complexes of WPW type, ventricular premature beats, and increased S-T segment depression. The P-R and P-J intervals are 0.02 second shorter as compared to the intervals in the same lead in Figure 1, while the QRS duration remains the same. C, record obtained soon after B shows resumption of original alternate type of WPW rhythm although the heart rate is still the same as in B.

likely for such regularly rhythmic fluctuations to continue for such long periods. It can, perhaps, be explained on the basis of concealed conduction. Retrograde incomplete penetration of the anomalous pathway by the impulse after activation of the ventricles can prevent stimulation of the anomalous path from the atrial end by the next impulse which is, therefore conducted via the normal path only. The next impulse again passes down both the pathways causing pre-excitation. Occurrence of tachycardias in WPW syndrome has been explained on the basis of complete penetration and continuation of such a re-entry mechanism.

Occurrence of WPW syndrome in patients with coronary arterial disease has been frequently reported. In the present case, the predominant symptom of progressive exertional dyspnea and the electrocardiographic changes on admission suggested a diagnosis of congestive heart failure due to coronary artery disease, although the tachycardia was rather out of proportion. A careful clinical search failed to reveal any evidence of thyrotoxicosis although it must be admitted that basal metabolic rate was not determined at the time. Relief of the symptoms and considerable decrease of heart rate with disappearance of the WPW beats after administration of digitalis were interpreted as confirming this diagnosis. That the manifestations were apparently caused by masked hyperthyroidism[8] and thyrotoxic heart

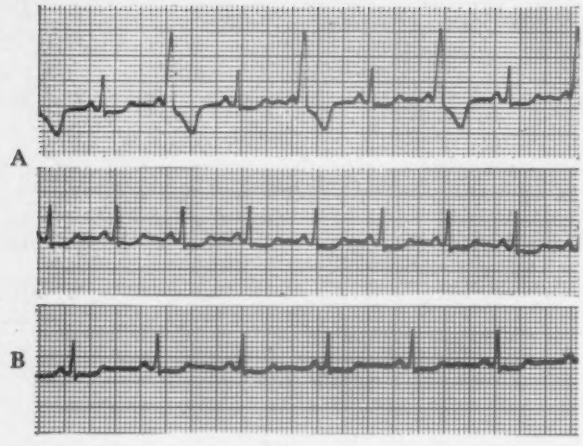


FIG. 3. (Lead II.) A, electrocardiogram taken on December 15 after administration of digitalis for ten days. The heart rate is 115 per minute. Upper strip shows alternate WPW beats. Lower strip shows spontaneous change to normal conduction without change of heart rate. Digitalis effect is shown by S-T segment depression. QRS duration in WPW beats is the same as in Figure 1. B, electrocardiogram taken on December 27 showing normal conduction in all the beats. The heart rate is 88 per minute.

disease became evident only when enlargement of the thyroid and other manifestations of hyperthyroidism appeared four months later. After relief of hyperthyroidism the exercise test was negative and presence of coexistent coronary arterial disease was considered unlikely.

Effects of vagal stimulation and of digitalis on the WPW syndrome have not been uniform, and different explanations have been offered for the variable effects. Carotid sinus pressure has sometimes been reported to cause slowing of the sinus rate or sinus arrest with escape of the nodal pacemaker and A-V dissociation, delayed conduction at the A-V node with wider QRS, increase of rate of conduction through the A-V node and narrower QRS, or appearance of WPW beats.[2,4–6,9–13] In one instance[14] it changed constant WPW conduction to an alternate one. In our case, each time carotid sinus pressure was applied, there occurred a pause followed by change from alternate WPW conduction to normal conduction in all the beats, with resumption of the original alternate rhythm after release of pressure. This action can be interpreted to indicate initial suppression of the impulse formation by the sinus pacemaker followed by suppression of conductivity of the anomalous pathway.

Digitalis and other vagomimetic drugs often cause apearance of WPW beats or widening of the QRS of WPW beats.[2,4,7,9,10,15–18] It

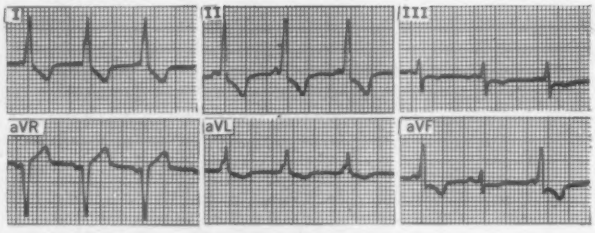


Figure 4. Electrocardiogram taken on December 17 after administration of digoxin for twelve days, showing all beats of WPW type up to lead aVL, and spontaneous change to alternate WPW beats in lead aVF. The heart rate is 100–108 per minute.

is believed that these drugs, by depressing the A-V node and the normal A-V pathway beyond a critical level, facilitate the appearance of the anomalous conduction. Such an explanation does not seem plausible because the concept of anomalous pathway implies that anomalous conduction takes place before normal conduction and it is difficult to imagine how depression of a normal path can facilitate conduction along the anomalous path.[19] Appearance of anomalous beats after digitalis has also been stated to be probably due either to bradycardia because of increase of stroke volume or disappearance of fatigue in the aberrant pathway, or to increase in myocardial irritability.[2] This would favor the concept of a hyperexcitable ventricular focus in the causation of WPW syndrome. Failure of digitalis to block the anomalous mechanism in cases of atrial fibrillation with fast runs of anomalous beats and appearance of anomalous beats after administration of digitalis have been considered by Wolff and Richman[10] as inconsistent with the notion that digitalis suppresses the anomalous conduction. Other investigators[4,13,14,20] have, however, observed disappearance of the WPW beats after digitalis. Scherf and Schonbrunner[20] attributed this to a greater affinity of the drug for the anomalous than for the normal pathway. Wolff and White[4] were unable to say whether this was due to digitalis. Gitsios[14] advanced the hypothesis that if the abnormal pathway over which the impulse bypasses the A-V node arises in the uppermost part of the node, it could be suppressed after administration of digitalis with interruption of the abnormal mechanism because of the action of the drug on the A-V node, and that the failure or success of digitalis in suppressing the abnormal conduction is not a matter of specificity for one or the other pathway, but depends rather on the structure, origin and direction of the abnormal pathway. This

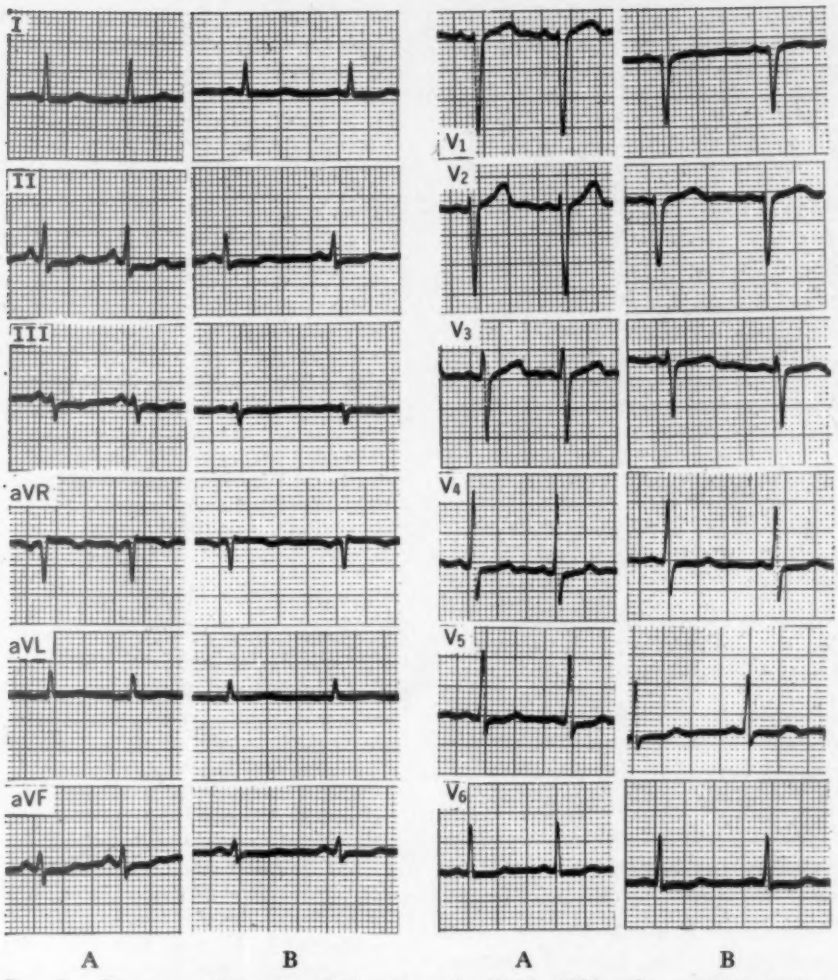


FIG. 5. Electrocardiograms obtained on April 24, 1959, after administration of digoxin for more than four months, (A) and on July 27, 1959, after administration of methylthiouracil for nearly three months (B). Both records show all normally conducted beats.

hypothesis, however, does not explain the appearance of the anomalous beats after digitalis.

In our case, on one occasion during the administration of digitalis, change to constant WPW conduction was seen to occur. Such a change was never seen to occur spontaneously although it was noted after exercise. It may, therefore, be attributed to digitalis and may be interpreted to indicate either increased conductivity of the anomalous pathway or increased irritability of a ventricular focus. Ultimately, however, after administration of the drug for two weeks, the anomalous beats disappeared, to reappear again five days after discontinuing the drug. The abolition of WPW conduction in our case was therefore obviously attributable to digitalis. This is against the theory of an irritable ventricular focus and can be interpreted to indicate suppression of conductivity of the anomalous path.

Exercise has been observed to cause acceleration of conduction in the normal A-V pathway resulting in a shorter and more normal QRS with pseudonormalization, the P-R interval remaining short.[2,19,21] True normalization may occur also which may be explained by assuming that at high heart rates either the conduction in an anatomic aberrant pathway does not take place because of fatigue, or that the mechanical effect of atrial contraction is smaller because of the decreased stroke volume.[2,19] Appearance of WPW beats after exercise has also been reported,[2,22] perhaps because of increased stroke volume.[2] In the present case exercise not only caused further acceleration of the already rapid heart rate, but also caused WPW conduction in successive beats, shortening of the P-R and P-J intervals while the QRS duration remained unaltered, and appearance of ventricular premature beats of a different configuration. A

few minutes later alternate WPW rhythm reappeared without, however, any change of the heart rate. This showed that exercise further facilitated conduction in the anomalous pathway rather than causing accelerated conduction in both the normal as well as the anomalous pathway. It was also clear that constant WPW type of conduction was not related to the heart rate which was, therefore, obviously due to the effect of exercise on the anomalous conduction. After administration of digitalis when normal conduction was firmly established exercise failed to produce WPW type of conduction, showing that digitalization counteracted the effect of exercise.

Disappearance of the anomalous beats after relief of hyperthyroidism in our case suggested an acquired genesis of the beats due to increased myocardial irritability. There is markedly increased sensitivity of the heart muscle to epinephrine under the influence of the thyroid hormone which intensifies the physiologic effects of epinephrine on the heart.[1] In the present case it is conceivable that a latent anomalous pathway existed but that the property of conductivity of this bypass with appearance of alternate WPW beats became manifest only when there occurred adrenergic preponderance due to the influence of abnormal thyroid function. Exercise which is known to increase adrenergic preponderance thus caused successive WPW beats. Thus, the WPW syndrome may be considered to represent not only an anatomic disturbance but also a physiologic one with some kind of an autonomic imbalance which can be influenced by the endocrine system, particularly the thyroid. Lown et al.[23] have suggested possible relationship between the endocrine system (particularly the adrenals) and autonomic nervous system on the one hand and the syndrome of short P-R interval, normal QRS complex and paroxysmal tachycardia on the other. It would be interesting to know whether in patients with the WPW syndrome the anomalous beats can be abolished by antithyroid drugs or whether in those with latent WPW syndrome anomalous beats can be precipitated by administration of thyroid hormone.

Summary

A case of WPW syndrome associated with thyrotoxicosis is reported. The WPW beats alternated with normally conducted beats. Exercise caused WPW conduction in successive beats. The arrhythmia could be terminated temporarily each time by carotid sinus pressure. It was abolished after continued administration of digitalis, and later, of methylthiouracil. It is suggested that conduction in a pre-existing latent anomalous bypass became manifest as a result of adrenergic preponderance due to hyperthryroidism, and that WPW syndrome may represent not only an anatomic disturbance but also a physiologic one which can be influenced by endocrine hormones.

Acknowledgment

Dr. L. R. Sarin, Superintendent, Sawai Man Singh Hospital, kindly permitted the publication of this report.

References

1. Raab, W. Hormonal and Neurogenic Cardiovascular Disorders, pp. 37, 133. Baltimore, 1953. Williams & Wilkins Co.
2. Lepeschkin, E. Modern Electrocardiography, pp. 353, 355, 361. Baltimore, 1951. Williams & Wilkins Co.
3. Strong, J. A. Thyrotoxicosis with ophthalmoplegia, myopathy, Wolff-Parkinson-White syndrome, and pericardial friction. *Lancet*, 1: 959, 1949.
4. Wolff, L. and White, P. D. Syndrome of short P-R interval with abnormal QRS complexes and paroxysmal tachycardia. *Arch. Int. Med.*, 82: 446, 1948.
5. Pick, A. and Katz, L. N. Disturbances of impulse formation and conduction in the pre-excitation (WPW) syndrome. Their bearing on its mechanism. *Am. J. Med.*, 19: 759, 1955.
6. Katz, L. N. and Pick, A. Clinical Electrocardiography, the Arrhythmias, p. 681. Philadelphia, 1956. Lea & Febiger.
7. Fox, T. T., Weaver, J. and March, H. W. On the mechanism of the arrhythmias in aberrant atrioventricular conduction (Wolff-Parkinson-White syndrome). *Am. Heart J.*, 43: 507, 1952.
8. Likoff, W. B. and Levine, S. A. Thyrotoxicosis as the sole cause of heart failure. *Am. J. M. Sc.*, 206, 425, 1943.
9. Blinder, H., Burnstein, J. and Smelin, R. Drug effects in Wolff-Parkinson-White syndrome. *Am. Heart J.*, 44: 268, 1952.
10. Wolff, L. and Richman, J. L. The diagnosis of myocardial infarction in patients with anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome). *Am. Heart J.*, 45: 545, 1953.
11. Rosenbaum, F. F., Hecht, H. H., Wilson, F. N. and Johnston, F. D. The potential variations of the thorax and the esophagus in anomalous atrioventricular excitation. *Am. Heart J.*, 29: 281, 1945.
12. Fisch, C., Pinsky, S. T. and Shields, J. Wolff-Parkinson-White syndrome. Report of a case associated with wandering pacemaker, atrial tachycardia, atrial fibrillation and incomplete A-V dissociation with interference. *Circulation*, 16: 1004, 1957.
13. Barker, J. M. Unipolar Electrocardiogram, p. 569. New York, 1952. Appleton-Century-Crofts, Inc.
14. Gitsios, C. T. Restoration of normal conduction

following administration of digitalis in a case of WPW syndrome. *Am. Heart J.*, 59: 283, 1960.
15. Wilson, F. N. A case in which the vagus influenced the form of the ventricular complex of the electrocardiogram. *Arch. Int. Med.*, 36: 1008, 1915.
16. Fox, T. T. and Robb, A. L. On the mechanism of the electrocardiographic syndrome of short P-R interval with prolonged QRS complex. *Am. Heart J.*, 28: 311, 1944.
17. Vakil, R. J. Transitory W-P-W aberration after intravenous strophanthin. *Brit. Heart J.*, 17: 267, 1955.
18. Fox, T. T., Travell, J. and Molofsky, L. Action of digitalis on conduction in the syndrome of short P-R interval and prolonged QRS complex. *Arch. Int. Med.*, 71: 206, 1943.
19. Lepeschkin, E. The Wolff-Parkinson-White syndrome and other forms of pre-excitation. In: Cardiology. An Encyclopedia of the Cardiovascular System, Vol. 3, pp. 94, 95. Edited by Luisada, A. A. New York, 1959. McGraw-Hill.
20. Scherf, D. and Schonbrunner, E. Beitrage zum Problem auf der verkurzton Vorhofkammer Leitung. *Ztschr. klin. Med.*, 128: 750, 1935.
21. Hejtmancik, M. R. and Herrmann, G. R. The electrocardiographic syndrome of short P-R interval and broad QRS complexes. A clinical study of 80 cases. *Am. Heart J.*, 54: 708, 1957.
22. Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W. and Kruger, H. E. The Auricular Arrhythmias, p. 285. Springfield, Illinois, 1952. Charles C Thomas.
23. Lown, B., Ganong, W. F. and Levine, S. A. The syndrome of short P-R interval, normal QRS complex and paroxysmal rapid heart action. *Circulation*, 7: 693, 1952.

A-V Dissociation with Interference in Partial Heart Block*

NELLY SZILAGYI, M.D., LEO M. TARAN, M.D., F.A.C.C.† *and* BENJAMIN RICHMAN, M.D., F.A.C.C.

Brooklyn, New York

ATRIOVENTRICULAR dissociation in partial heart block is a condition in which atria and ventricles act independently of each other and in which the ventricular rate is faster than the rate of the "conductible" atrial impulses. In A-V dissociation with interference, circumstances are such as to favor at times conduction of atrial excitations. The first description of this arrhythmia in partial heart block, based on jugular and arterial pulse curves, was given by Mobitz[1] in 1923. The first description of electrocardiographic curves demonstrating A-V dissociation with interference in several cases of 2:1 block and one case of 3:1 block was published by Dressler[2] in 1929. A-V dissociation was first described in English by Zeisler[3] in 1932. The complexities of its mechanism and a critical and comprehensive review of the literature were the subject of recent publications.[4,5]

The case to be presented is of interest not only because of the rarity of A-V dissociation with interference in, presumably, 3:1 block, but also because it permits the estimation of the refractory period of the bundle with great accuracy, and because the long duration of the high grade block affords a suitable opportunity to observe fluctuations in refractoriness of the conduction system and their influence on the arrhythmia in a series of electrocardiograms.

CASE REPORT

E. G., an eighty-four year old white woman, was admitted with a history of recurrent high grade A-V block. The electrocardiogram on admission revealed regular sinus rhythm, the pattern of right bundle branch block and possible concomitant left ventricular hypertrophy. T wave changes were suggestive of ischemia of the anterior wall. Three months after admission the patient had another episode of high grade block which lasted about three months. Shortly after its onset, the patient had an Adams-Stokes seizure from which she recovered spontaneously. During the period of high-grade block, a series of electrocardiograms were taken; the pertinent findings are summarized in Table 1.

A-V Dissociation with Interference in Partial A-V Block: The electrocardiographic tracing of January 13, 1959 has been selected to illustrate A-V dissociation with interference in partial heart block. Figure 1 is part of lead II of this record. The fundamental rhythm is a sinus rhythm. The P waves are evenly distributed at intervals ranging from 0.66 to 0.74 second. The predominant sequence of ventricular cycles is periodically interrupted by cycles of shorter duration terminating in QRS complexes of somewhat different contour. The QRS complexes R_2, R_3, R_5, R_6, R_8, R_9, R_{11}, R_{12}, R_{14}, R_{15}, R_{17}, and R_{18}, terminating the longer cycles, show no fixed relation to the preceding P waves, indicating A-V dissociation. These QRS complexes are fairly regularly spaced at intervals ranging from 1.60 to 1.66 seconds; their contour differs from that of sinoatrial beats in the lower amplitudes of the R and S waves. These complexes represent automatic beats. Every third cycle is of shorter duration, ranging from 1.52 to 1.58 seconds. The QRS complexes R_4, R_7, R_{10}, R_{13}, R_{16}, and R_{19} which terminate these shorter cycles do resemble sinoatrial beats. They are preceded by P waves in the identical P-R interval of 0.14 second. These beats apparently are conducted sinus beats.

P_3, P_5, P_{10}, P_{12}, P_{17}, P_{19}, P_{24}, P_{26}, P_{31}, P_{33}, P_{38} and P_{40}, occurring at R-P intervals ranging from 0.96 to 1.25 seconds, reached the bundle when it was still in the refractory state due to the passage of the preceding conducted or automatic beat and were, therefore, blocked. P_1, P_8, P_{15}, P_{22}, P_{29}, P_{36} and P_{43} occurred late in diastole at R-P intervals ranging from 1.38 to 1.44 seconds. These atrial excitations arrived at the bundle after complete recovery of its conductivity from the passage of the preceding automatic beat and were conducted to the ventricles. Their R-P intervals are longer than double the sinus

* From the Brooklyn Hebrew Home and Hospital for the Aged, Brooklyn, New York.
† Deceased.

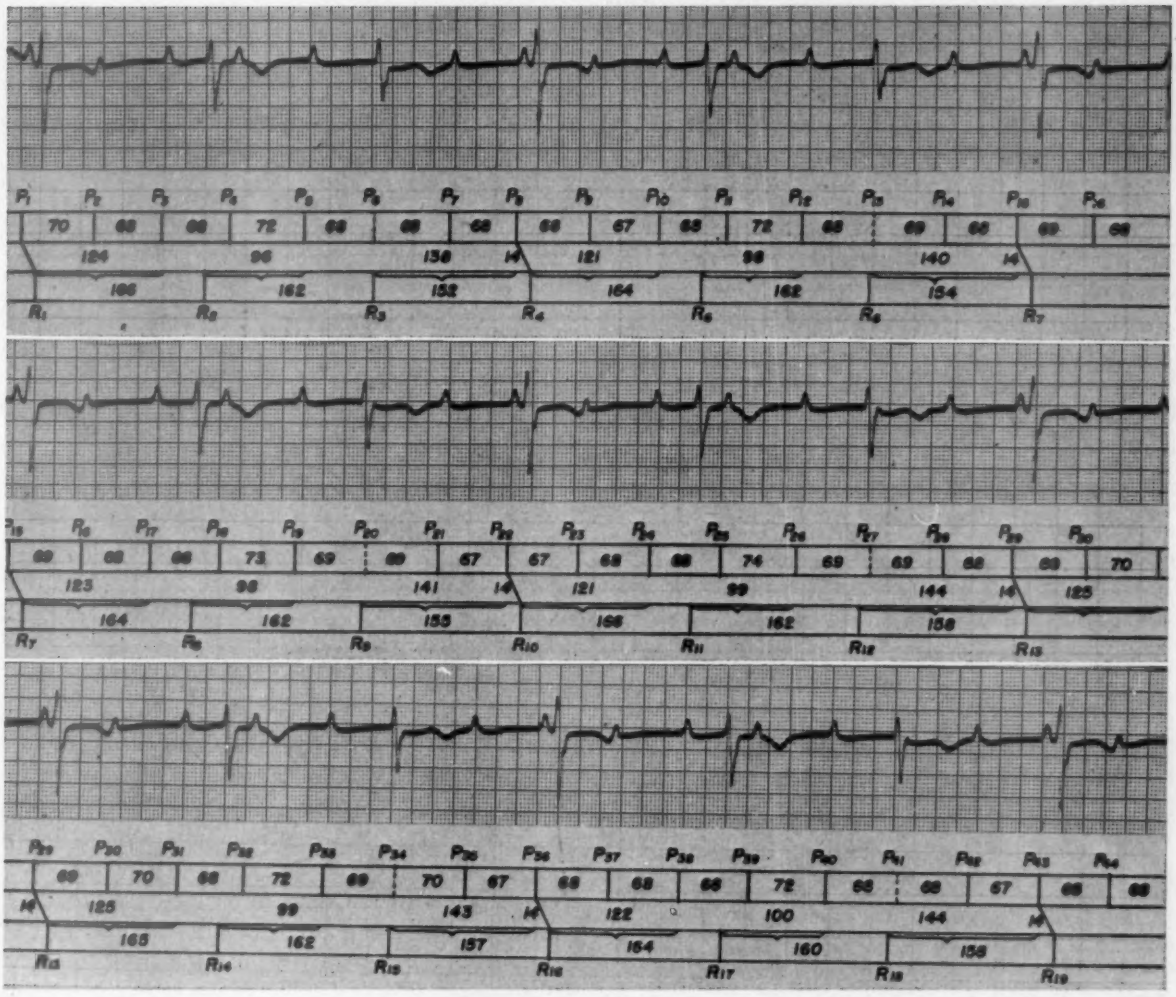


FIG. 1. Continuous strip of lead II of the tracing of January 13, 1959. The last cycle in each line is reproduced at the start of the next line. The strip illustrates A-V dissociation with interference in the presence of, presumably, 3:1 block. The regular automatic rhythm is periodically interrupted by premature beats (R_4, R_7, R_{10}, R_{13}, R_{16}, R_{19}) of sinoatrial origin. P waves occurring late in diastole were conducted to the ventricles; those occurring at an R-P interval of 1.23 seconds and less were blocked. The R-P interval of the conducted sinus beats is longer than double and shorter than three times the atrial period, suggesting 3:1 block underlying the A-V dissociation.

period and shorter than three times this period, suggesting 3:1 block underlying the A-V dissociation.

These features satisfy the criteria of Dressler, Roesler and Specter[6] for the recognition of A-V dissociation with interference in partial block, which in this case presumably is a 3:1 block.

Transition from 2:1 Block to A-V Dissociation: Figure 2 is part of lead aVF of the same record as Figure 1, and illustrates the transition from 2:1 block to A-V dissociation. R_1 through R_4 are the last of a long series of conducted sinus beats in atrial half-rhythm 2:1 A-V block; the R-P intervals of the conducted P waves (P_2, P_4, P_6, P_8) range from 1.24 to 1.27 second. P_{10}, which occurred only 0.01 second earlier than the earliest of these, namely, at an R-P interval of 1.23 seconds, was blocked. The next impulse, P_{11}, presumably would have been conducted to the ventricles, changing 2:1 into 3:1 ratio; however, the automatic impulse of R_5 was discharged ahead of P_{11} and rendered the bundle refractory. The escape beat of R_5 initiated A-V dissociation which is interfered with by the conducted sinus beats of R_7 and R_8. A new short series of sinus beats (R_{11} through R_{15}) follows the A-V dissociation, showing a 2:1 rhythm. The R-P intervals of the conducted P waves (P_{24}, P_{26}, P_{28}, P_{30}, P_{32}) range from 1.23 to 1.25 seconds. P_{34}, which arrived at 1.25 second, that is, 0.01 second later than the conducted impulse of P_{32}, and 0.02 second later than P_{26}, found the bundle refractory and was, therefore, blocked. The escape beat of R_{16} again prevented the formation of a block of a higher order than 2:1. R_{19} is the first conducted beat of a longer series in atrial half rhythm.

Comparison of the R-P intervals of the conducted P waves in the last cycle of each series of 2:1 rhythm with those of blocked P waves in the first automatic cycle in nine instances led to findings identical to

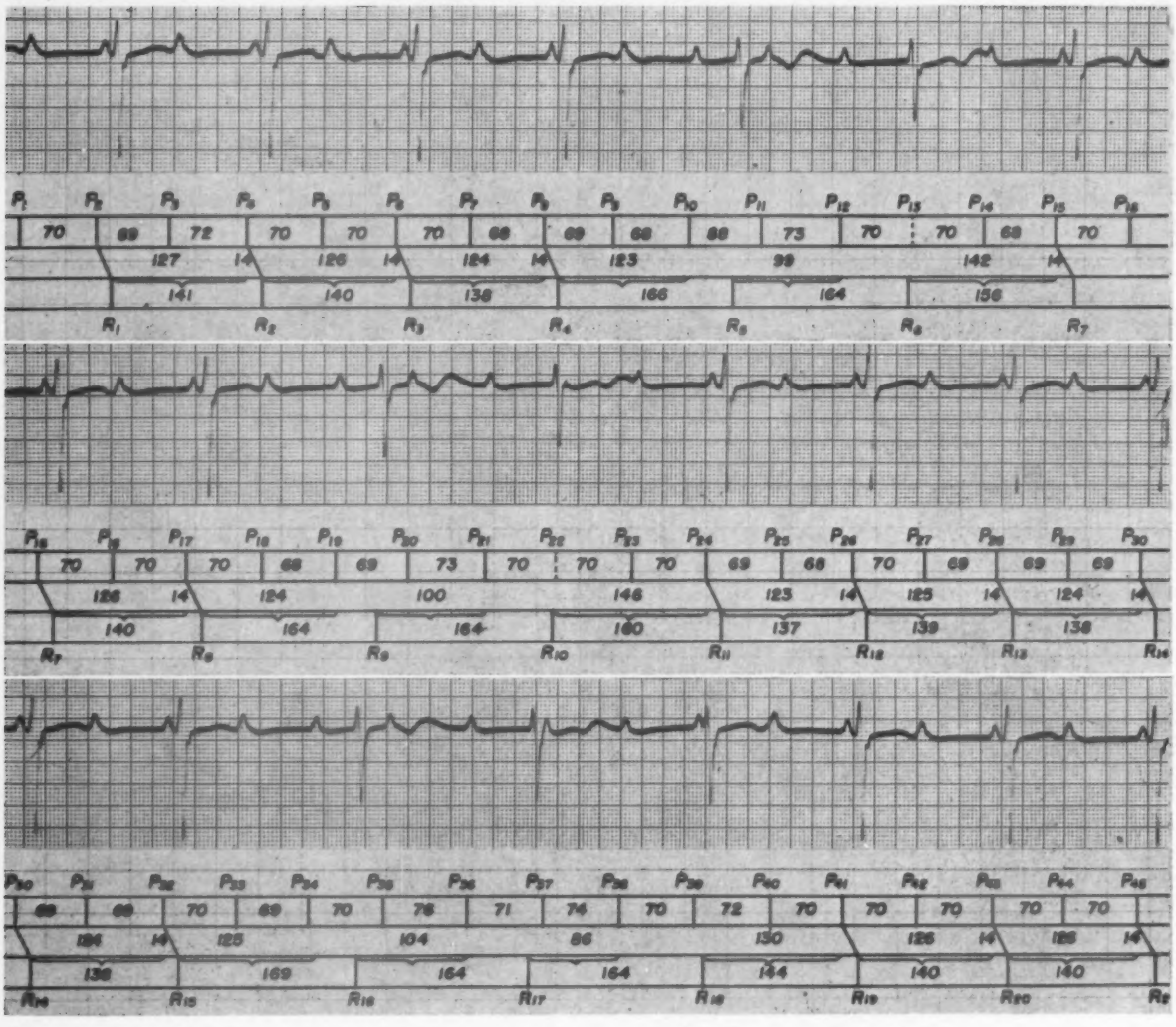


FIG. 2. Continuous strip of lead aVF of the same record as Figure 1. The last cycle of each line is repeated at the start of the next line. The strip illustrates the transition from 2:1 block to A-V dissociation. P_{26} is conducted at the shortest R-P interval in the record of 1.23 seconds. P_{10}, occurring at an identical R-P interval, and P_{24}, occurring only 0.02 second later, are blocked. The duration of the refractory period fluctuates between 1.23 and 1.25 seconds.

those illustrated in Figure 2. In six out of these nine instances, atrial excitations were not conducted at the expected time, indicating that the refractory period was not yet terminated. In three instances, P waves arrived earlier by not more than 0.02 second and were blocked, indicating that the bundle was still refractory. "The critical R-P interval which separates blocked from conducted sinoauricular impulses,"[6] and which is an approximate measure of the refractory period of the bundle, is 1.23 seconds. Conducted and nonconducted P waves overlap in the range of R-P intervals from 1.23 to 1.25 seconds, suggesting minimal spontaneous fluctuation in refractoriness.

COMMENT

Variations in the conduction disorder were observed in a series of electrocardiograms during a recurrence of high grade A-V block, associated with fluctuations in refractoriness due to the labile state of the diseased conduction system. We also observed variations of the rhythm within the same record which were conditioned by the peculiar relation of the refractory period to the duration of the auricular cycle.

For no obvious reason, the refractory period lengthened from a duration of about double the atrial cycle (January 13, 1959) to one exceeding that value by far (January 14, 1959), leading to complete A-V dissociation. Refractoriness remained at this high level in the subsequent tracings. The nature of the conduction disturbance could not be ascertained at the time the tracings were recorded. Any one of the following mechanisms might have been the

TABLE I
Summary of Electrocardiographic Findings*

Date	Ventricular Complex	Rhythm	Range of Intervals (in 1/100 sec.)		R-P Intervals (in 1/100 sec.)	
			P-P	R-R Automatic Beats	Shortest Conducted P (critical)	Longest Non-Conducted P
1/12/59	Right BBB, LVH† Ischemic T wave	Bigeminy diss interf in 3:1 block	60–64	166–188	128	134
1/13/59	Regression of T wave changes	2:1 block	68–72			
		Diss interf in 3:1 block	66–76	156–170	123	125
1/14/59	Unchanged	Compl diss	68–72	172–182	...	168
1/17/59	Unchanged	Compl diss	80–84	172–186	...	168
1/19/59	Unchanged	Compl diss	72–80	184–190	...	172
Isoproterenol		Compl diss	46	136–146	...	128
	Shortened Q-T	3:1 block	44		120	...
		Compl diss	44	132–140	...	118
		3:1 block	44		120	...
		Compl diss	52–54	136–144	...	130
		Diss interf in 3:1 block	54–56	140–152	128	...
	Return to previous Q-T	Compl diss	78–84	180–188	...	164
1/26/59	Unchanged	Compl diss	86–94	184–196	...	172
2/ 5/59	Regression of T	Diss interf in 3:1 block	74–70	176–182	152	152
2/17/59	...	Compl diss	76–84	188–192	...	178
2/24/59	Return of T to pattern before attack	Diss interf in 3:1 block	58–70	172–184	138	142
3/ 6/59	Unchanged	Compl diss	76–88	194–196	...	172
4/ 5/59	Unchanged	RSR	86–90	...	...	...

* This table lists the pertinent findings of each electrocardiogram of the series showing a recurrence of high grade block. In addition, it lists changes induced by isoproterenol (0.2 mg. subcutaneously) on January 19, 1959. Electrocardiographic samples were taken for a period of two hours. Data are given for all points of change of rhythm and all of the pertinent intervals in chronologic order.

† Left ventricular hypertrophy confirmed at autopsy. Abbreviations: Diss interf = A-V dissociation with interference; Compl diss = complete A-V dissociation; RSR = regular sinus rhythm; BBB = bundle branch block.

cause: (1) A-V dissociation with partial heart block; (2) intermittent complete heart block; and (3) permanent complete heart block. (Because of its lesser chances of Adams-Stokes seizures, the latter would have been preferred.) Isoproterenol was administered in a dose of 0.2 mg. subcutaneously. At the height of the effect of the drug 3:1 block was recorded alternating with short periods of A-V dissociation (Table I). When the effect was wearing off, A-V dissociation with interference in presumably 3:1 block was noted. A-V dissociation with interference reappeared spontaneously and was recorded in the tracings of February 5 and February 24, 1959. Three months later regular sinus rhythm was present and persisted for several months.

In two tracings striking alterations in rhythm were observed which were associated with small fluctuations in P-P interval and in the duration of the refractory period such as may occur in the normal conduction system. In the tracing of January 13, 1959 (Figs. 1 and 2), the duration of the refractory period of the bundle was apparently close to twice the atrial cycle; atrial excitations arriving 0.01 second too early found

the bundle refractory and were blocked. Small prolongations of the refractory period of about 0.02 second had the same effect on the rhythm and 2:1 block was transformed into presumed 3:1 block underlying the A-V dissociation. A similar close relation of the duration of the refractory phase to a multiple (three times, in this case) of the atrial cycle was transiently noted in the tracing of January 19, 1959, at the height of the effect of isoproterenol. At this stage, runs of 3:1 block alternated with periods of complete A-V dissociation. Shortening by not more than 0.02 second of the R-P interval of the atrial excitation expected to be conducted caused a transition from 3:1 ratio to a presumably 4:1 ratio underlying the runs of A-V dissociation.

Summary

Electrocardiograms are presented illustrating the following: (1) A-V dissociation with interference in the presence of partial block, presumably 3:1 block; and (2) the transition from 2:1 block into A-V dissociation.

The duration of the refractory period could be determined with great accuracy.

When the refractory period was close to two or three times the atrial period, minimal alterations of the P-P interval affecting only one atrial period or minimal alteration of the refractory period caused the transformation of 2:1 or 3:1 block into A-V dissociation.

At the height of the effect of isoproterenol, 3:1 block alternated with complete A-V dissociation. This stage was followed by a period of A-V dissociation with interference in, presumably, 3:1 block. Two hours after administration of the drug measurements had returned to the level present before isoproterenol.

References

1. Mobitz, W. Zur Frage der atrioventrikularen Automatie. Die Interferenzdissoziation. *Deutsches Arch. klin. Med.*, 141: 257, 1923.
2. Dressler, W. Dissoziation und Interferenzen bei partiellem Herzblock. *Ztschr. klin. Med.*, 111: 23, 1929.
3. Zeisler, E. B. A-V dissociation. *J. Lab. & Clin. Med.*, 18: 225, 1932.
4. Miller, R. and Sharrett, R. H. Interference dissociation. *Circulation*, 16: 803, 1957.
5. Marriott, H. J. L., Schubart, A. F. and Bradley, S. M. A-V dissociation: a reappraisal. *Am. J. Cardiol.*, 2: 586, 1958.
6. Dressler, W., Roesler, H. and Specter, L. S. Dissociation with interference in the presence of 2:1 atrioventricular block. *Am. Heart J.*, 44: 238, 1952.

Direct Electrocardiographic Recording of a Twenty-three Millimeter Human Embryo*

REUBEN STRAUS, M.D., RALPH H. WALKER, M.D. *and* MORRIS COHEN, PH.D.

Burbank, California

THE OPPORTUNITY to record and study certain fundamental biomedical phenomena in human material is seldom available in routine practice. Because of the availability of specialized equipment† we were able to secure a direct electrocardiographic tracing on a 23 mm. human embryo. A survey of the literature has revealed a paucity of information pertaining to electrocardiographic activity in such early human embryos, and for this reason we report our observations in one such case.

TECHNIC OF RECORDING

Incidental to a therapeutic hysterectomy in a pregnant patient, we secured an embryo 23 mm. in crown-rump length (Fig. 1). At surgery the uterine arteries were clamped as the final step in the hysterectomy prior to the incision of the vaginal cuff. This resulted in a fifteen-minute period of independent intrauterine survival which was followed by a nine-minute period of exposure to air prior to the beginning of the electrocardiographic recording. During the latter period and the final eleven minutes of survival, the surface of the embryo was moistened intermittently with warm saline and warmed continuously with a 150 watt sunlamp at a distance of about three feet.

The electrocardiographic recording apparatus consisted of a transistorized Sanborn EEG/ECG preamplifier, Model 55, attached to a Sanborn Viso Cardiette, Model 51, set on lead I. Sensitivity of the latter was standardized so that 1 mv. produced a 1 cm. deflection. Twenty-gauge hypodermic needles, silver-plated to prevent polarization, were employed as electrodes (Fig. 2). The preamplifier was standardized to yield a deflection of 8.5 mm. per 100 μv. at an attenuator setting of 5×. The low frequency cut-off was set at 1.5 c.p.s. and the high frequency cut-off at 20 c.p.s. The attenuator of the preamplifier was initially set at 10×, each mm. deflection being equivalent to 24 μv., and during later recording altered to 5×, when the amplitude of the tracing decreased, whereby each mm. deflection then became equivalent to 12 μv.

The standard procedures for the placement of the electrodes could not be employed. Whereas it was intended that these be lateral chest leads, it was subsequently confirmed that the negative electrode was inserted into the left lateral abdominal wall and the positive electrode just medial to the right eye. The ground lead was inserted into the perineum (Fig. 2).

DESCRIPTION OF ELECTROCARDIOGRAM‡

Segments of the tracing are illustrated in Figure 3, from which classic P, QRS, T configurations can be seen. The entire electrocardiographic complex consisted of a P wave of 0.02 second, P-R interval of 0.20 second, a QRS complex of 0.18 second and a T wave of 0.22 second (Fig. 3A). The individual components were also characterized by the following deflections: the P wave upright with an amplitude of 9 μv., no Q wave but an R wave of 26 μv.; a deep S wave of 405 μv., and an upright T of 140 μv. The S-T segment was slurred. At the outset, the heart rate was approximately 40 per minute but occasionally was found to vary up to 80 per minute (Fig. 3B, C, E, H). Despite the arrhythmia, no distinctive change in the character of the individual components was detected.

After the first minute of recording, an occasional dropped beat was observed (Fig. 3C, E, F). A noticeable dissociation between the P wave and the remainder of the complex (Fig. 3D, E) could also be seen. Multiple premature atrial discharges were noted, some only 0.24 second apart (Fig. 3D, E). When the QRS appeared responsive to the P wave excitation there was progressive increase of the P-R interval, from 0.20 to 0.32 second, followed by a dropped QRS complex suggesting a Wenkebach

† Preamplifier, designed for fetal cardiography and electroencephalography, was purchased for our study of high altitude hypoxia, supported by Grant No. RG-5657 from Division of Research Grants, National Institutes of Health, Public Health Service.

‡ Assistance of Richard Halpern, M.D., in the study of the electrocardiograms is gratefully acknowledged.

* From the Saint Joseph Hospital, Herbert and Vera Yates Department for Medical Research, Burbank, California.

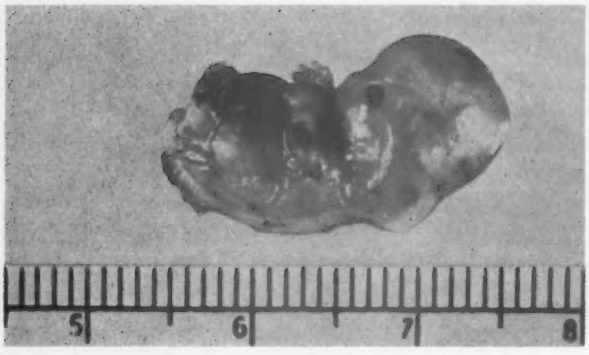


FIG. 1. Embryo of approximately seven to seven and one-half weeks gestation measuring 23 mm. crown-rump length in the fresh state.

phenomenon (Fig. 3E). After 2.5 minutes of recording, the arrhythmia became more pronounced, the rate varying from approximately 40 to 80 per minute (Fig. 3F, G, H). Associated with this, the amplitude of the S wave diminished to 256 μv. and the T wave to 105 μv. The S-T configuration varied slightly, revealing a more horizontal segment which at times was isoelectric and at other times depressed (Fig. 3E, F, G, H). During periods of reduced cardiac rhythm, the injection of isoproterenol or cooling caused temporary restoration of rhythm and change in configuration of the tracing toward the "normal" (Fig. 3F, H).

After about five minutes (Fig. 3I), the P wave was unchanged, the P-R interval increased to 0.32 second, the QRS was unchanged except for a further decrease to 152 μv., the T wave was shortened to 0.08 second and was of 23 μv. amplitude. The rate at that time was 80 per minute. Because of this reduction in the electrical output of the heart, the attenuation was decreased to 5× (Fig. 3J). It was possible thereby to secure again tracings with satisfactory peak responses so that even after an interval of six minutes, all of the components of a typical tracing were recognizable and measurable. At this time the following values for the different components were established: P wave, 0.02 second; P-R interval, 0.28 second; and the QRS interval, 0.06 second. As the record progressed (Fig. 3K) certain deviations in the S-T and T wave were also observed. Occasionally (Fig. 3L) further arrhythmia was noted characterized by the rapid succession of three to four complexes followed by a long pause.

It is interesting that removal of the warming light bulb to allow cooling (Fig. 3M) restored the cardiac rate to about 80 per minute and the tracing tended toward the initial configuration for short intervals. This was followed by a gradual slowing to 60 per minute, during which the take-off for the T wave remained high but the wave became inverted.

After intrathoracic injections of 0.2 ml. isoproterenol, the S-T segment frequently became isoelectric for periods lasting for as long as fifty seconds (Fig. 3N). Normal sinus rhythm reappeared, with atrial waves

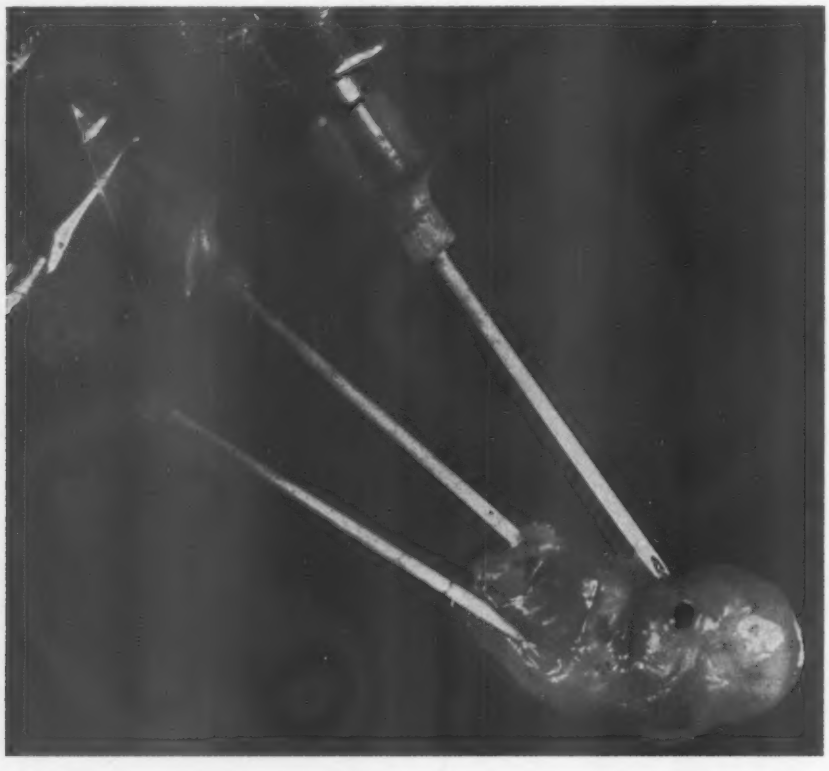


FIG. 2. Twenty-three millimeter embryo with silver plated 20-gauge needles serving as the electrocardiographic leads.

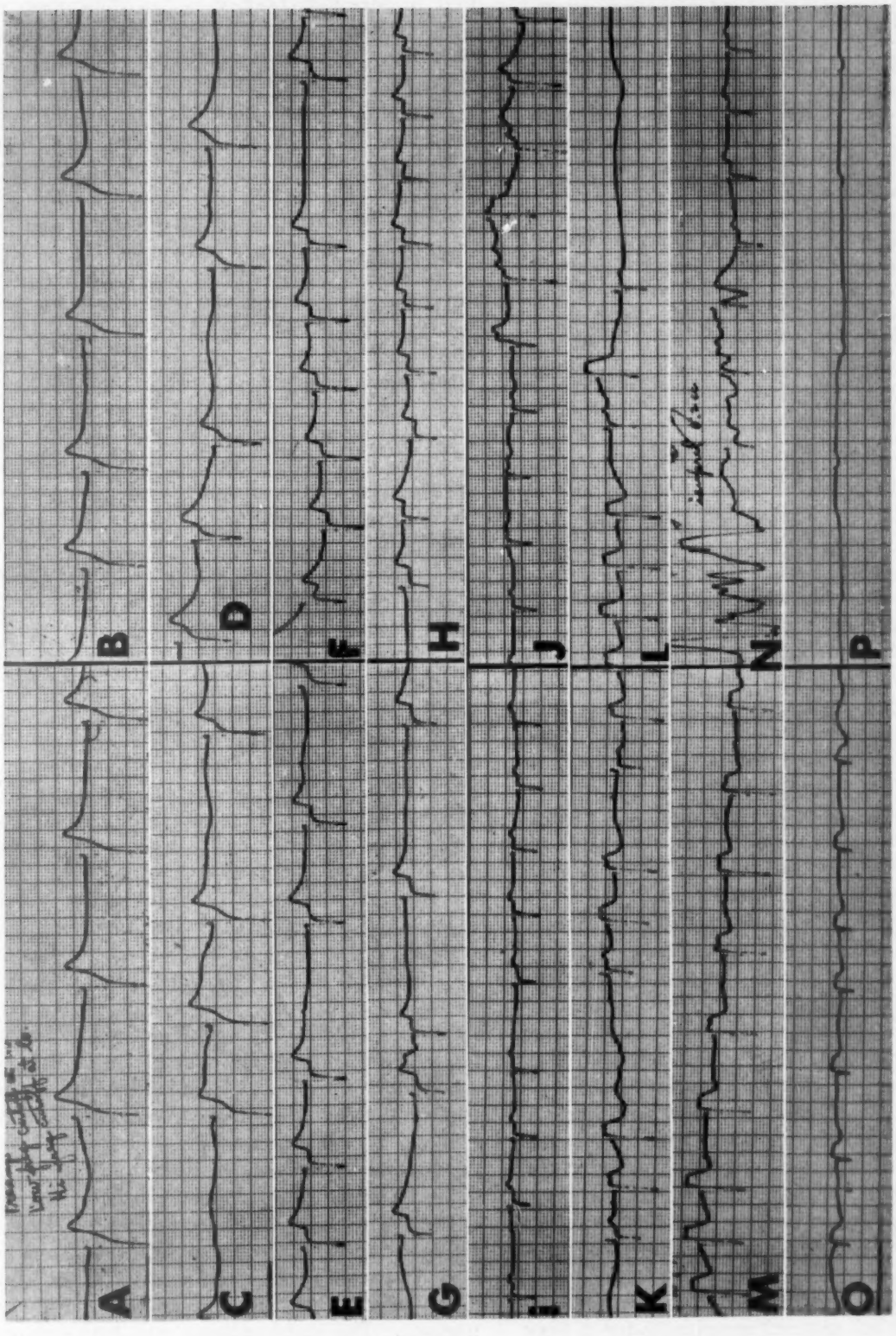


FIG. 3. Segments of a continuous electrocardiographic tracing secured on a 23 mm. embryo. A, initial tracing; B, fifteen seconds; C, forty-five seconds; D, one and one- quarter minutes; E, two and three-quarter minutes; F, three minutes; G, three and three-quarter minutes; H, four and one-quarter minutes; I, five and one-quarter minutes; J, five and three-quarter minutes; K, six minutes; L, five and one-quarter minutes; M, seven minutes; N, eight minutes; O, nine and one-quarter minutes; and P, twelve and one-quarter minutes.

occurring at 80 per minute with occasional sino-atrial pauses and interpolated premature atrial beats.

Toward the end of the record, at $9^1/_4$ minutes, the P waves disappeared entirely and the S waves were reduced in amplitude to only 46 μv. (Fig. 3O). The T wave take-off was elevated 12 μv., the T wave inversion persisted, and finally the T wave disappeared. The last configuration to disappear completely was the RS complex which showed no appreciable change in rate but a marked decrease in amplitude to 12 μv. (Fig. 3P). Terminally, the rate was 60 per minute and rhythmic. Upon the injection of 0.10 ml. isoproterenol at the tenth minute of the record, the small electrical impulses reappeared for approximately twelve to fifteen seconds. In the terminal segment of the pattern an occasional small deflection would appear, but even these finally ceased. Further injection of isoproterenol produced no response.

Comments

Direct electrocardiographic tracings of human embryos and fetuses have been secured in very few instances.[4–8] The youngest of these embryos from which electrical activity has been claimed to have been recorded is reported by Marcel and Exchaquet.[8] They observed occasional "contractions of the heart" in a "two week" old, 6 mm. embryo and secured only slight deflections on an electrocardiographic tracing. Since embryologically the heart only begins to be formed at about the third week[1,9] it is reasonable that the myocardial contractions must start some time thereafter. Furthermore, a more reliable criterion for myocardial contractility would appear to be objective recording of electrical activity rather than visual inspection. It is doubtful, therefore, that the "two week" old embryo actually yielded a cardiac electric potential in the usual sense.

The same authors[8] did secure a tracing exhibiting the "classical elements of the electrocardiographic tracing of the adult" on a " four week" old embryo. From the reported "15 mm. diameter" of that specimen it would appear that the more probable age was 5.5 weeks.[11] Furthermore, considering the fact that the development of the heart is incomplete prior to the seventh week, it is highly interesting that the electrocardiographic tracing of a 5.5 week old embryo could exhibit a normal adult configuration.

Goodyer[5] reported briefly on an electrocardiographic tracing secured terminally for a very short interval on an 18 mm. embryo, approximately seven weeks of age, but the tracing was reported not to be characteristic of the adult type.

Considerable uncertainty exists regarding the determination of precise age of these embryos. From the obstetrical history, the embryo observed by us was estimated to be 7.5 weeks of age. From measurement of the crown-rump length, according to Streeter's charts,[11] a 23 mm. embryo should be approximately of eight weeks menstrual age or 6.5 weeks ovulatory age. Its presumed age is estimated to lie between these extremes and coincides with the menstrual age determined from the obstetrical history.

All of the classic elements of the adult electrocardiogram were recognized in our specimen which is consistent with the fact that at this embryonic age the heart has developed into the adult four-chambered structure.[1,9] However, appreciable differences can be seen in the electrocardiographic pattern of the embryo compared to that of the adult, particularly with reference to cardiac rate, electrical potential and the character of the P wave and S-T segment.

Usually the intrauterine heart rate of the human fetus is in the vicinity of 117 to 158 per minute[5,10,13] On the other hand, extrauterine heart rates of human embryos have been reported, and also observed by us, to vary from 20 to 100 per minute.[3–6,8] The markedly reduced rates under these conditions can be ascribed, in part, to viability and to environmental factors, such as the initial drop in temperature after hysterectomy, which is suggestive of a direct correlation between temperature and heart rate. Our observations revealed additionally an anomalous response between embryonic heart rate *ex situ* and further cooling in that an increased rate was noted following removal of the heat source. With the absence of additional direct experimental data we are inclined to interpret this response as a compensatory reaction to peripheral tissue anoxia, i.e., a mitigation of the effects of hypoxia, produced by cooling. These responses suggest further that even at this early age, the human embryo is in possession of a neural or humoral cardiac regulatory mechanism.

The magnitude of deflection of the elements of the electrocardiographic complex is influenced by heart mass, electrode positioning, thickness and character of intervening tissues and sensitivity and standardization of the sensing apparatus. For these reasons, absolute comparisons cannot be made of the electropotentials reported in the literature to be generated by

embryonic and fetal hearts. Reported electropotentials[2] of 7 to 90 μv. of the fetal heart *in situ* secured through the maternal body wall cannot possibly be representative of the actual potential since the fetal electrocardiogram is superimposed on the maternal electrocardiogram with consequent reinforcement or suppression of amplitude as well as being influenced by intervening tissues. Our own direct measurement of energy output revealed a maximum deflection of 405 μv. for the S wave. By contrast, the adult heart develops an energy output of 2,000 to 3,000 μv.[2] although outputs of only 200 μv. have been considered within normal limits.[12]

Some of the P-R and QRS intervals, 0.20 and 0.08 second, respectively, for the fetal electrocardiogram approximate those noted in the adult tracing, a finding also noted by Heard et al.[6] Since the size of the embryonic heart is so much smaller than that of the adult and the conduction system proportionately shorter, the propagation of the excitation wave in the embryo heart must be considerably slower than in the adult. Whether or not this is related to an interrupted or incomplete conduction system or to the physical-chemical character of embryonic tissue is at present not apparent.

Additional interpretations of our electrocardiographic tracings cannot be made at this time. Some of the observed phenomena are held in common with electrocardiographic tracings of hearts of patients dying of noncardiac causes. Additional studies of human embryonic hearts must be made before the physiologic significance of the variations in the tracings can be firmly established.

Summary

An electrocardiographic recording of a human embryo approximately seven weeks of age has been described. Evidence is presented for the existence of a functionally complete cardiac system with respect to the electrocardiographic components. Some physiologic responses are reported and the possible existence of a myo-, neuro- or humoral regulatory mechanism is suggested.

References

1. Arey, L. B. A Textbook and Laboratory Manual of Embryology, 5th ed., p. 325. Philadelphia, 1946. W. B. Saunders.
2. Bergman, P. and Hall, P. Pre-natal foetal electrocardiography. *Acta obst. et gynec. scandinav.*, 37: 348, 1958.
3. Blondheim, S. H. Technique of fetal electrocardiography. *Am. Heart J.*, 34: 35, 1947.
4. Easby, M. H. Electrocardiograms from a four and half months old fetus. *Am. Heart J.*, 10: 118, 1934.
5. Goodyer, A. V. N. Clinical Prenatal Electrocardiography. Thesis submitted for M.D. degree, 1942, Yale University.
6. Heard, J. D., Burkley, G. G. and Schaefer, C. R. Electrocardiograms derived from eleven fetuses through the medium of direct leads. *Am. Heart J.*, 11: 41, 1936.
7. Hon, E. H. The fetal heart rate patterns preceding death in utero. *Am. J. Obst.*, 78: 47, 1959.
8. Marcel, M. P. and Exchaquet, J. P. L'electrocardiogramme du foetus humain avec un cas de double rythme auriculaire verifie. *Arch. mal. coeur, Paris*, 31: 504, 1938.
9. Patten, B. M. Human Embryology, pp. 125–129, 656–673. New York, 1953. Blakiston Co.
10. Soiva, K. and Salmi, A. Phonocardiographic studies of the foetal heart rate. *Ann. chir. et gynaec. Fenniae*, 48: 287, 1959.
11. Streeter, G. L., Heuser, C. H. and Corner, G. W. Developmental horizons in human embryos. *Contrib. Embryol.*, 34: 167, 1951.
12. Wilson, F. M., Rosenbaum, F. F. and Johnston, F. D. Interpretation of the ventricular complex of the electrocardiogram. In: Advances in Internal Medicine, p. 56. Edited by Dock, W. and Snapper, I. New York, 1947. Interscience Publishers.
13. Wong, M. and Cassels, D. E. The fetal electrocardiogram. *J. Dis. Child.*, 99: 20, 1960.

Atrial Dissociation*

RAMON F. ABARQUEZ, M.D. *and* JOHN S. LA DUE, M.D., F.A.C.C.

New York, New York

THE EXISTENCE in man of atrial dissociation has been doubted by White[1] and implied to be artefactual by Katz.[2] Although clinical examples of atrial dissociation are few, convincing proofs that atrial dissociation does occur in man have been presented by Decherd[3] and Deitz[4] and their co-workers.

In 1920 Schrumpf[5] published the first electrocardiograms of atrial dissociation occurring in a patient with congestive heart failure and digitalis toxicity. The ventricular conducted P wave was 64 per minute while p′ wave which was not conducted to the ventricle had an independent rate of 109 per minute. More recently, Dimond and Hayes[6] described atrial dissociation following ventricular standstill.

The purpose of this paper is to report on a patient with myocardial infarction and embolism to the lungs, brain and right femoral artery, who exhibited atrial dissociation for three days before death.

CASE REPORT

A sixty-five year old white woman was admitted on May 18, 1959, to Memorial Center for right radical mastectomy for Paget's disease of the breast. Preoperatively the patient was given 1.2 mg. of digitoxin orally and 0.1 mg. on alternate days for four days. Digitoxin was continued postoperatively in the same maintenance dose for seventeen days until three days before death when glycoside was given intramuscularly.

The postoperative period was complicated by bronchopneumonia which subsided after a week of penicillin-streptomycin therapy. The patient was afebrile and asymptomatic for more than a week when suddenly on the seventeenth postoperative day she became dyspneic, cyanotic and hypotensive, but had no chest pain or hemoptysis. The serum glutamic oxalacetic transaminase (SGO-T) was 291 units, and the electrocardiogram on June 11 as contrasted with that on May 21 (Figs. 1 and 2) showed S-T segment depression and T wave inversions in leads I, II, III, aVL, aVF and V_3 to V_6; peaked P waves in leads II, III and aVF; and diphasic P wave in V_1 and V_2. A low to flat P wave was present in leads I and aVL, with P-Q segment depressions in leads II, III and aVF and slight P-Q segment elevation in lead aVL. Atrial dissociation was also noted for the first time (Fig. 3).

The patient was placed on anticoagulant therapy on June 11, 1959. The next day she became semicomatous and left-sided hemiplegia developed. The electrocardiogram showed further S-T segment depressions and T wave inversions with the appearance of S waves from leads V_1 to V_6. The SGO-T was 444 units. Atrial dissociation persisted (Fig. 4). On June 13 P waves in leads V_1 and V_2 became monophasic and upright, S-T segment was isoelectric and T waves were upright in leads I, II, III, aVF, aVL and V_3 to V_6. S waves were no longer recorded in leads V_5 and V_6. Atrial dissociation still existed (Fig. 5). A few hours before death the right foot was cold, cyanotic and pulseless. Anuria and hyperkalemia were present before death. Permission for postmortem examination was denied.

COMMENTS

This patient had atrial dissociation for three consecutive days in the presence of sinus rhythm without any atrioventricular block. The electrocardiograms demonstrated two parallel sets of atrial activation. The P wave which was transmitted to the ventricles was almost three times faster than p′ wave which did not activate the ventricles. There was no clinical evidence of digitalis toxicity.

Mechanism: It has been suggested[4] that in atrial dissociation each atrium beats separately and independently of the other as a result of interruption of an interatrial pathway (Bachmann's bundle).[8] This concept does not agree with the experiments of Prinzmetal et al.[7] who demonstrated that both atria and the interatrial septum are anatomically and physiologically inseparable. If the mechanism of atrial dissociation is a blocked interatrial pathway, a sinus activated atrial P wave should be transmitted to only one atrium. Both atria can only be activated by a sinus pacemaker if it is

* From the Department of Cardiology, Memorial Center for Cancer and Allied Diseases, New York, New York.

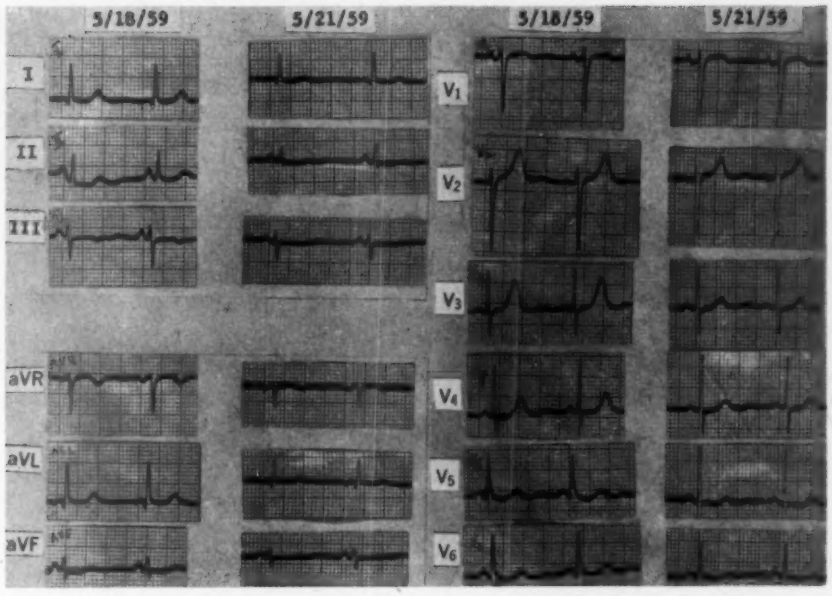


FIG. 1. *May 18, 1959.* Electrocardiogram taken on admission prior to digitalization. Tracing is within normal limits. *May 21, 1959.* Tracing before surgery and after digitoxin therapy. ST-T changes suggest digitalis effect.

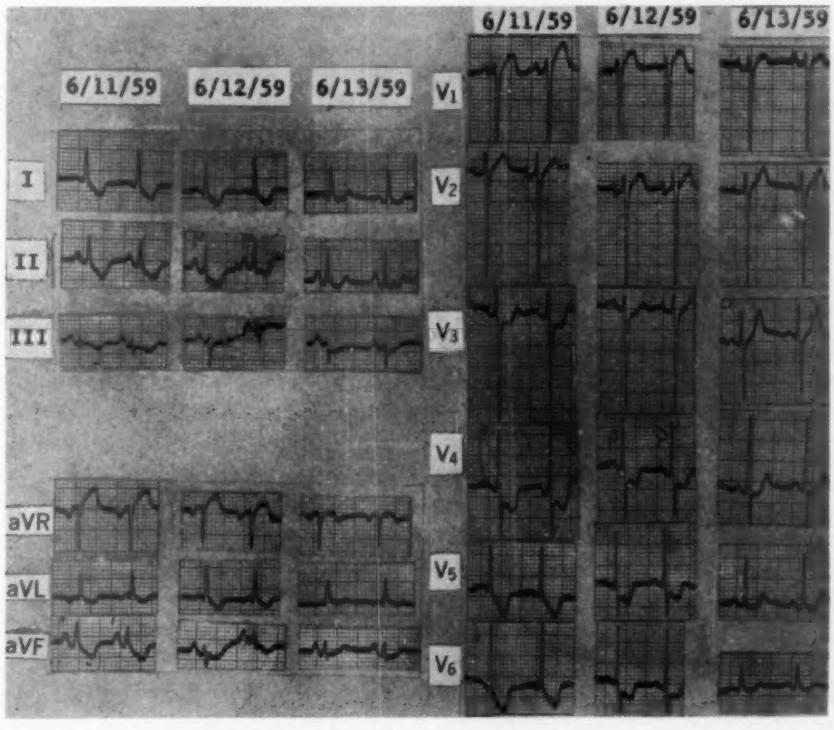


FIG. 2. These tracings show changes compatible with atrial infarction and subendocardial ischemia. Evidence of atrial dissociation is seen in the records of *June 12 and 13.*

assumed that impulses can be perpetuated to the other atrium despite an interatrial block. It has been shown that blocks between the left and the right atria created by experimentally produced tissue destruction[7,8] did not alter the experimentally produced atrial arrhythmias.

A possible explanation of the mechanism of atrial dissociation is that, in addition to the normal P wave conducted by the sinoatrial node, another independent focus from either atrium exists which is capable of depolarizing only its limited immediate area. Such a p′ wave may

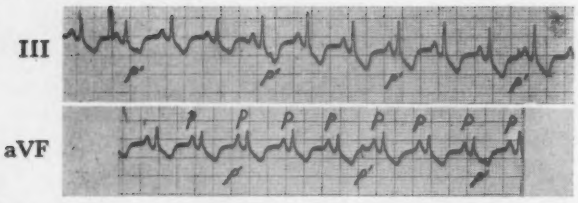


FIG. 3. *June 11, 1959.* Leads II and aVF show atrial dissociation. Sinus activated atrial wave is labeled P. Ectopic and dissociated uniatrial activation is shown as p′. Sinus rate is 120/min. Dissociated atrial beat rate is 42/min.

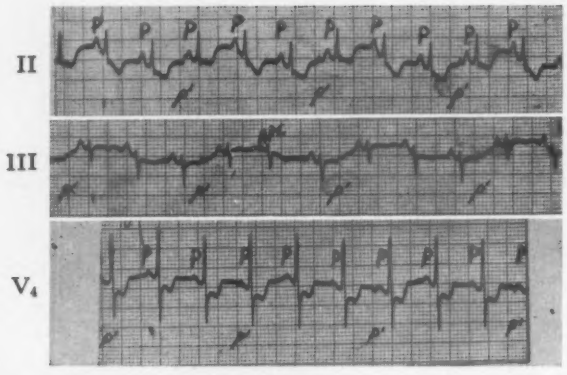


FIG. 4. *June 12, 1959.* Leads II, III and V_4 demonstrate persistent atrial dissociation.

be due either to a weak ectopic focus during the nonrefractory period, or to a stronger impulse occurring when the rest of the atrial musculature is refractory. The nonrefractory period is short and the stimuli at the ectopic site ineffective when the basic rate is rapid.[7] Thus during flutter and fibrillation, stimuli from other ectopic foci which might have caused extrasystoles during normal sinus rhythm cannot be effective. This diminutive ectopic focus does not interfere with the dominant rhythm and may have no physiologic effect since it is not being transmitted to the ventricles. This mechanism, uniatrial para-arrhythmia,[4] may exist together with a sinus rhythm as demonstrated by our patient.

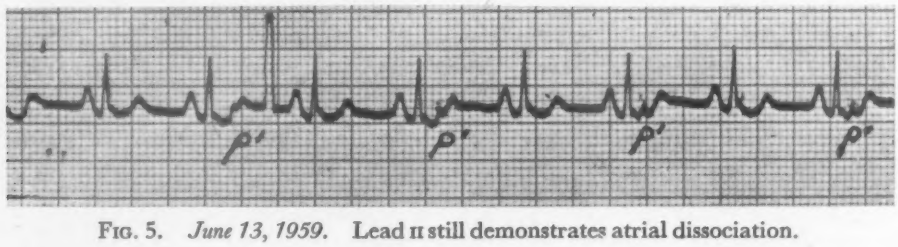


FIG. 5. *June 13, 1959.* Lead II still demonstrates atrial dissociation.

From the conventional 12-lead electrocardiogram, P waves from analogous portions of the right and left atria have the same configuration.[7] For that reason any attempt at localization of p′ wave as arising either from the right or left atrium would be erroneous if not impossible.

Association with Atrial Infarction: Reviews by Decherd et al.[3] and Deitz et al.[4] of the literature on atrial dissociation show no distinct correlation with the clinical status of the patients. Atrial dissociation has been reported in patients who had digitalis toxicity,[4,5] rheumatic heart disease,[5,9,10] glomerulonephritis,[5] acute and chronic coronary thrombosis,[11,12] adenomatous goiter and partial thyroidectomy,[13] and it has been reported in elderly patients,[14] a normal nine year old girl[15] and a normal six day old infant.[16] The case of Scherf and Siedek[12] suggested that the interatrial artery may have been occluded. Since experimental atrial dissociations were produced by occluding the artery supplying Bachmann's bundle[12] and by ligation of the atrial artery,[17] atrial infarction should be suspected in the presence of atrial dissociation.

The most reliable clue to the clinical diagnosis of infarction of the atria is abnormality in the atrial mechanism.[18] In 74 per cent of patients with atrial infarction and in only 9 per cent with ventricular infarction, abnormalities of the atrial complexes were noted in the electrocardiogram. In 17 per cent of 182 cases of ventricular myocardial infarction proved at autopsy atrial infarction was also present.[18] P-Q segment depression or elevation was noted experimentally[18–22] and clinically[22–31] in atrial infarction, and occurred in 22 per cent of proved atrial infarctions.[18] On the other hand, Shipley and Hallaran,[32] Stewart and Manning[33] and Copeland et al.[34] showed that P-Q segment changes may occur in normal subjects. The P-Q segment may be depressed in patients with emphysema[35–37] or arterial hypertension.[38] Experimentally, P-Q segment elevations and depressions were produced following necrosis of the atria[39] although no electrocardiographic changes occurred after temporary occlusion of

the right atrial vessels.[17] Other electrocardiographic evidences of experimental and clinical atrial infarction are P wave changes consisting of broadening, inversion, a decrease or increase in amplitude, slurring, notching, atrial "q" or "s" waves, or "M" or "W" complexes.[18,20,23,40] All these are not specific changes of atrial infarction because experimentally[18,41] and clinically,[23,42] atrial infarction may be demonstrated only by atrial arrhythmia without P wave or P-Q segment changes. The diagnosis of atrial infarction should be suspected in any patient with acute myocardial infarction or arteriosclerotic heart disease in whom atrial arrhythmia suddenly develops with or without the P wave and P-Q segment abnormalities just described.

The patient presented herein had electrocardiographic changes suggestive of atrial infarction (low and almost flat P waves in leads I and aVL, changes in configuration of P wave in leads V_1 and V_2, P-Q segment depression in leads II, III and aVF, and slight P-Q segment elevation in lead aVL). The high SGO-T, in the absence of other conditions associated with elevated SGO-T, indicated ventricular infarction although the electrocardiographic evidence was equivocal. The appearance of atrial dissociation in this patient may have resulted from the suspected atrial infarction.

Summary

Atrial dissociation of three days' duration is described in a patient who had normal atrioventricular conduction. Acute atrial infarction associated with ventricular myocardial infarction may have precipitated the observed atrial dissociation.

References

1. White, P. D. Heart Disease, 4th ed., p. 931. New York, 1951. The Macmillan Co.
2. Katz, L. N. Electrocardiography, 2nd ed., p. 772. Philadelphia, 1946. Lea and Febiger.
3. Decherd, G. M., Jr., Ruskin, A. and Brindley, P. Interatrial and sinoatrial block. *Am. Heart J.*, 31: 352, 1946.
4. Deitz, G. W., III, Marriott, H. J. L., Fletcher, E. and Bellet, S. Atrial dissociation and uniatrial fibrillation. *Circulation*, 15: 883, 1957.
5. Schrumpf, P. De l'interference de deux rhythmes sinusaux; preuve du dualisme du nodule de Keith. *Arch. mal. coeur*, 13: 168, 1920.
6. Dimond, E. G. and Hayes, W. L. An electrocardiographic demonstration of atrial dissociation. *Am. Heart J.*, 56: 929, 1958.
7. Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W. and Kruger, H. E. The Auricular Arrhythmias, pp. 18, 45, 74, 270. Springfield, Ill., 1952. Charles C Thomas.
8. Brams, W. A. and Katz, L. N. The nature of experimental flutter and fibrillation of the heart. *Am. Heart J.*, 7: 249, 1931.
9. Bay, E. B. and Adams, W. Possible intranodal block. A report of cases. *Am. Heart J.*, 7: 759, 1932.
10. Mahaim, I. De l'aneurisme primitif de l'oreillette gauche, troubles particuliers du rhythme cardiaque; la dissociation interauriculaire. *Ann. méd.*, 21: 380, 1927.
11. Lian, C. and Golbin, V. Un cas de double rhythme auriculaire par dissociation interauriculaire. *Arch. mal. coeur*, 31: 52, 1938.
12. Scherf, D. and Siedek, H. Über Block zwischen beiden Vorhofen. *Ztschr. klin. Med.*, 127: 77, 1934.
13. Hertz, J. A case of double auricular action with one sided block. *Acta. med. Scandinav.*, 101: 409, 1939.
14. Geraudel, E. La double commande: étude des traces où coexistent deux commandes indépendantes, l'une auriculoventriculaire, l'autre auriculaire. *Arch. mal. coeur*, 28: 121, 1935.
15. Duclos, F. Un caso de "doble comando auricular." *Arch. cardiol. y hemat.*, 16: 175, 1935.
16. Dominguez, C. and Bizzozero, R. C. Double commande auriculaire. *Arch. mal. coeur*, 30: 820, 1937.
17. Condorelli, L. Experimentelle Untersuchungen uber die interaurikulare Reizleitung. *Ztschr. ges. exper. Med.*, 68: 516, 1929.
18. Cushing, E. H., Feil, H. S., Stanton, E. J. and Wartman, W. S. Infarction of the cardiac auricles. *Brit. Heart J.*, 4: 17, 1942.
19. Abramson, D. I., Fenichel, N. M. and Shookhoff, C. Study of electrical activity in auricles. *Am. Heart J.*, 15: 471, 1938.
20. Sanders, A. Experimental localized auricular necrosis; electrocardiographic study. *Am. J. M. Sc.*, 198: 690, 1939.
21. Wenger, R., Massumi, R. A. and Kuramoto, K. Comparative study of esophageal and direct auricular electrocardiography in dogs. *Cardiologia*, 26: 193, 1955.
22. Corsi, V., Sangiorgi, M. and Corelli, D. Contribution to electrocardiographic localization of auricular myocardial damage; experimental study. *Cardiologia*, 23: 255, 1953.
23. Freundlich, J. and Sereno, L. R. Auricular infarction. *Am. Heart J.*, 57: 654, 1959.
24. Langendorf, R. Elektrokardiogramm bei Vorhof-Infarkt. *Acta. med. scandinav.*, 100: 136, 1939.
25. Young, E. W. and Koenig, A. Auricular infarction. *Am. Heart J.*, 28: 287, 1944.
26. Roberts, J. T. and Loube, D. S. Congenital single coronary artery in man. *Am. Heart J.*, 34: 188, 1947.
27. Hellerstein, H. K. Atrial infarction with diagnostic electrocardiographic findings. *Am. Heart J.*, 36: 422, 1948.
28. Soderstrom, N. Myocardial infarction and mural thrombosis in atria of heart. *Acta med. scandinav. suppl.*, 217: 7, 1948.
29. Gross, D. The auricular T-wave and its correlation to the cardiac rate and to the P-wave. *Am. Heart J.*, 50: 24, 1955.

30. Di Ielsi, A. M., Pinsky, H. A. and Eyonon, H. K. Auricular infarction: report of two cases. *Ann. Int. Med.*, 36: 640, 1952.
31. Miller, R. and Perelman, J. S. Multiple disturbances of rhythm and conduction and unusual auricular T-wave in a case of myocardial infarction. *Am. Heart J.*, 31: 501, 1946.
32. Shipley, R. A. and Hallaran, W. R. Four-lead electrocardiogram in 200 normal men and women. *Am. Heart J.*, 11: 325, 1936.
33. Stewart, C. B. and Manning, G. W. A detailed analysis of the electrocardiograms of 500 R.C.A.F. aircrew. *Am. Heart J.*, 27: 502, 1944.
34. Copeland, D. G., Tullus, F. I. and Brody, D. A. Clinical evaluation of a new esophageal electrode; with particular reference to the bipolar esophageal electrocardiogram. *Am. Heart J.*, 57: 862, 1959.
35. Wasserburger, R. H., Ward, J. G., Cullen, R. E., Rasmussen, H. K. and Juhl, J. H. The T-a wave of the adult electrocardiogram: an expression of pulmonary emphysema. *Am. Heart J.*, 54: 875, 1956.
36. Wasserburger, R. H., Kelly, J. R., Rasmussen, H. K. and Juhl, J. H. The electrocardiographic pentalogy of pulmonary emphysema. *Circulation*, 20: 831, 1959.
37. Zuckerman, R., Cabrera, E., Fishleder, B. L. and Sodi-Pallares, D. Electrocardiogram in chronic cor pulmonale. *Am. Heart J.*, 35: 421, 1948.
38. Hahn, L. P-R segment in hypertensive heart disease. *Brit. Heart J.*, 2: 101, 1940.
39. Hahn, L. and Langendorf, R. Zur Morphologie des Vorhof-Elektrokardiogramms. Rechtsund Links-Hyperfunktionstypus des Vorhof-Electrokardiogramms. *Acta med. Scandinav.*, 100: 279, 1939.
40. Abildskov, J. A. The atrial complex of the electrocardiogram. *Am. Heart J.*, 57: 930, 1959.
41. James, T. N. and Burch, G. E. The atrial coronary arteries in man. *Circulation*, 17: 90, 1958.
42. James, T. N. and Carrera, G. M. Pathogenesis of arrhythmias associated with metastatic tumors of the heart. *New England J. Med.*, 260: 869, 1959.

Diagnostic Shelf

Electrical Alternans in Association with Hemorrhagic Pericardial Effusion*

ROBERT L. CURRAN, M.D.

Providence, Rhode Island

ELECTRICAL ALTERNANS, a rare electrocardiographic abnormality, is generally defined as a regular alternation in direction or amplitude of any or all of the electrocardiographic complexes provided that the site of impulse formation remains constant. Thus, there are two alternating paths of conduction from one focus of impulse formation. Excluded by definition are regular alternation secondary to respiratory motion, bidirectional ventricular tachycardia and bigeminal rhythms.

Lewis, in 1911, first recorded this abnormality in a human subject who had paroxysmal atrial tachycardia.[1] Electrical alternans has been induced experimentally by ligation of a coronary artery, digitalis poisoning and the administration of hemolytic sera.[2] Colvin[3] in 1958 recorded only sixty-four cases in the literature. Hamburger et al.,[4] in 1936, noted an incidence of 1 in 10,000 electrocardiograms. In reviewing the past 72,000 electrocardiograms at the Rhode Island Hospital, ten cases were revealed. The most striking case is one of transient total electrical alternans in association with hemorrhagic pericardial effusion.

CASE REPORT

J. B., a fifty year old woman, was admitted to the Rhode Island Hospital for the third time on September 20, 1960. In 1956 a left simple mastectomy was performed at another hospital for carcinoma of the breast, and was followed by x-ray therapy. The patient remained well until June 1959. During her first admission to Rhode Island Hospital in September 1959, radiograms demonstrated an osteolytic lesion in the body of the third lumbar vertebra. Laboratory studies were unremarkable and the alkaline phosphatase was 11 units (King-Armstrong). A bilateral oophorectomy was performed. Metastatic carcinoma was demonstrated in the pathologic specimen. Subsequent therapy consisted of administration of androgens and steroids. Pain in the back caused her second admission in August 1960. Multiple metastatic lesions in the lumbar spine and pelvis were treated by regional radiation. Ten days prior to the third admission, the patient noted increasing abdominal girth. Progressive dyspnea began three days previous to admission.

Physical examination revealed a well-developed, chronically-ill white woman with moderate respiratory distress and orthopnea. Blood pressure was 120/94 mm. Hg with a 20 mm. paradoxical pulse as compared with a blood pressure of 150/90 on her previous admission. Pulse was 100. Pertinent findings included distention of the veins in the neck, dullness to percussion and absent breath sounds over the left side of the posterior section of the chest to the midscapula level extending across the axilla to the precordium, dullness and decreased breath sounds on the right side posteriorly, and the liver palpable 3 fingerbreadths below the right costal margin and extending across the epigastrium into the left upper quadrant. The heart sounds were easily audible and there were no murmurs, gallops or rubs.

A roentgenogram of the chest, when compared with previous films, demonstrated a marked increase in the size of the cardiac shadow and right and left pleural effusions (Fig. 1). An electrocardiogram demonstrated total electrical alternans (Fig. 2). Soon thereafter, when the blood pressure fell to 100/90, a pericardiocentesis via a left anterolateral approach was performed. Following the removal of 300 cc. of serosanguineous fluid, the blood pressure rose to 150/90 and the patient experienced relief of her dyspnea. Subsequent cytologic examination of the fluid demonstrated tumor cells. An electrocardiogram at the conclusion of the procedure demonstrated

* From the Department of Cardiology, Rhode Island Hospital, Providence, Rhode Island.

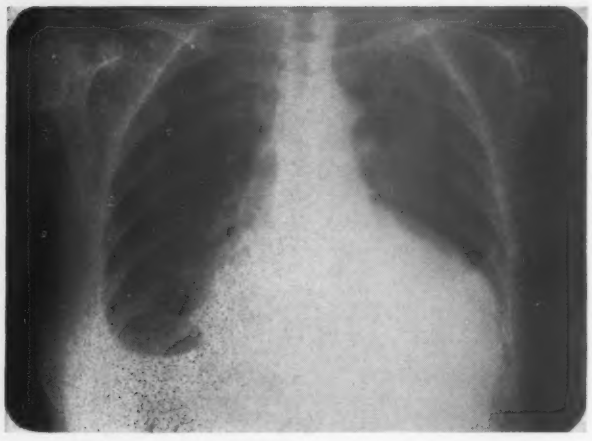


FIG. 1. Roentgenogram of the chest preceding the first pericardiocentesis demonstrating a large cardiac silhouette and right and left pleural effusion.

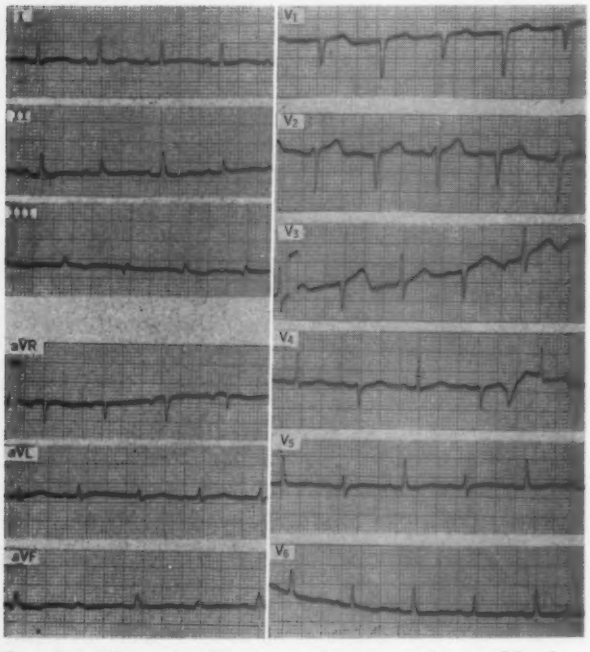


FIG. 2. Electrocardiograms demonstrating total electrical alternans. Alternation of the QRS complexes is seen in all leads, particularly the precordial leads. T wave alternation is best discerned in V_3. P wave alternation is most apparent in leads aVF, V_1 and V_2.

cessation of the electrical alternans (Fig. 3). On September 22, 1960 and September 23, 1960, left thoracenteses were performed with the removal of 1,300 cc. of serosanguineous fluid. On September 27, 1960, following a repeat pericardiocentesis with removal of 350 cc. of fluid (Fig. 4), 45 mg. of thio-tepa was instilled into the pericardial space. The patient was discharged to the care of her private physician.

COMMENTS

Electrical alternans in the presence of pericardial effusion has been recorded approxi-

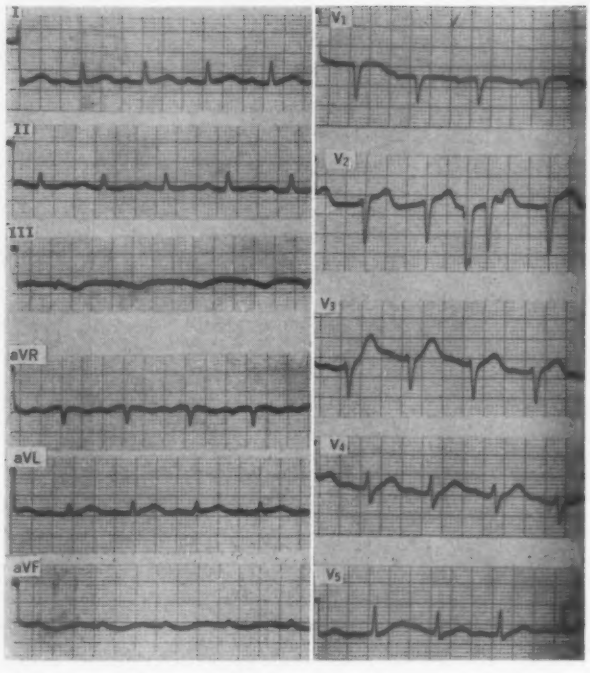


FIG. 3. Electrocardiogram immediately after first pericardiocentesis demonstrating cessation of total electrical alternans.

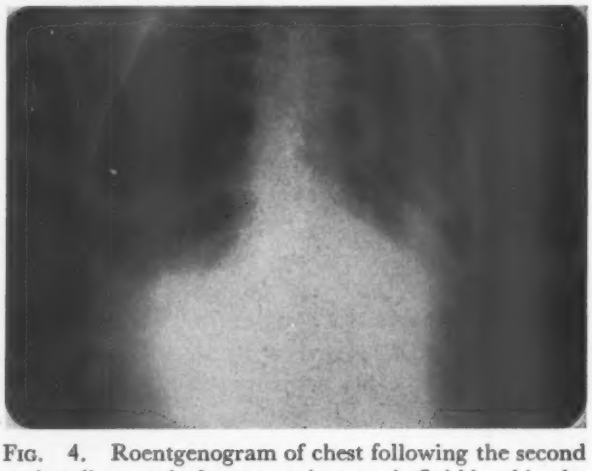


FIG. 4. Roentgenogram of chest following the second pericardiocentesis demonstrating an air-fluid level in the pericardial sac.

mately twenty-five times.[2,5–10] The phenomenon of total electrical alternans, alternation of all components of the electrocardiogram, has been described only sixteen times. As in the case at hand, it has always been noted in association with pericardial effusion, is always of a transient nature and usually disappears following pericardiocentesis. Feldman[5] reported the first case of electrical alternans in the presence of pericardial effusion in 1938, but Harvey and Whitehill[11] had previously described what may be presumed to be electrical alternans in association with tuberculous pericarditis.

Causes of Electrical Alternans in Pericardial Effusion: Baskind[9] was the first one to note the relationship of total electrical alternans with pericardial effusion. He and McGregor[9] proposed a theory, subsequently amplified by Littmann and Spodick,[10] to explain their observation. It is their hypothesis that in the presence of pericardial effusion, the heart, suspended by the great vessels, lies freely floating in the pericardial sac. Cardiac motion, normally restrained by contact with the mediastinal and pulmonary vessels, is unhindered. Usually with each contraction, the heart rotates counterclockwise on its longitudinal axis during systole and clockwise during diastole. With loss of mediastinal and pulmonary restraining forces secondary to the presence of the effusion the heart does not return to its normal diastolic position. The following systole adds rotational force to a partially rotated heart. In this manner a rhythmic cardiac oscillation ensues. The oscillatory rate varies with cardiac size, rate and position, as well as general body conformation. At a certain cardiac rate, usually in excess of 100, the frequencies of the oscillatory phenomenon and the heart rate form a 1:2 ratio, with the onset of total electrical alternans. When the heart rate is not a simple multiple of the oscillatory rate, irregular fluctuations in the electrocardiographic pattern may occur. Pericardiocentesis will cause a cessation of total electrical alternans by disturbing the relationship between heart rate and cardiac oscillation as well as by obviating the situation which initially produced the oscillation. Other mechanisms which may explain the cessation of electrical alternans despite the continued presence of pericardial effusion are increased viscosity of the pericardial fluid or the formation of adhesions from parietal to visceral pericardium.[7]

A second theory which has been used to explain the association of electrical alternans with pericardial effusion is that an increase in pericardial pressure causes decreased cardiac filling with consequent myocardial hypoxia secondary to diminished coronary blood flow. This concept was first proposed by Feldman in 1938,[5] but does not explain the relationship of total electrical alternans with pericardial effusion as well as the theory of McGregor and Baskind.

Summary

An unusual case of total electrical alternans in association with hemorrhagic pericardial effusion is presented.

Acknowledgment

I would like to express my appreciation to J. M. Gibson, Jr., M.D., for permission to report this case.

References

1. Lewis, T. Notes upon alternation of the heart. *Quarterly J. Med.*, 4: 141 1911.
2. Reisinger, J., Pekin, T. and Blumenthal, B. Primary tumor of the inferior vena cava and heart with hemopericardium and alternation of the ventricular complexes in the electrocardiogram. *Ann. Int. Med.*, 17: 995, 1942.
3. Colvin, J. Electrical alternans. A case report and comments on the literature. *Am. Heart J.*, 55: 513, 1958.
4. Hamburger, W., Katz, L. and Saphir, O. Electrical alternans. A clinical study with a report of two necropsies. *J. A. M. A.*, 106: 902, 1936.
5. Feldman, L. Electrical alternans occurring in a case with pericardial effusion. *Am. Heart J.*, 15: 100, 1938.
6. Traut, E. Alternans: report of a case associated with acute pericarditis. *Postgrad. Med.*, 8: 439, 1950.
7. Ström, O. Hemopericardium with electrical alternans. *Acta med. Scandinav.*, 164: 367, 1959.
8. Coley, A. and Schwartz, R. Disappearance of electrical alternans following pericardiocentesis. *Arch. Int. Med.*, 101: 577, 1958.
9. McGregor, M. and Baskind, E. Electrical alternans in pericardial effusion. *Circulation*, 11: 837, 1955.
10. Littmann, D. and Spodick, D. Total electrical alternation in pericardial disease. *Circulation*, 17: 912, 1958.
11. Harvey, A. and Whitehill, M. Tuberculous pericarditis. *Medicine*, 16: 45, 1937.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Complications of Open Heart Operations

DRS. WILLEM J. KOLFF, D. B. Effler and L. K. Groves have recently made clinical observations on 150 consecutive patients who underwent open heart operations. These were corroborated by laboratory experiments and were later confirmed in open heart operations of 400 consecutive patients. They describe four complications of open heart operations.*

1. *Acidosis* is most severe 3 or more hours after operation. It may be expected not only after open heart operations but also after other operations whenever a low cardiac output as evidenced by low blood pressure has been present for a considerable time.
2. *Overoxygenation.*
3. *Heart block* can occur after operations in the neighborhood of the atrioventricular bundle. It is no longer justifiable to undertake an open heart operation without a pacemaker at hand. Whenever heart block occurs, one electrode is sewn to the myocardium before the chest is closed, although the heart rate while the patient is on the operating table is still satisfactory.
4. *Pulmonary complications* in open heart operations can nearly always be avoided. The most important single preventive measure is the use of a wide cannula in the left atrium to measure the pressure in the left atrium, and to drain out blood into the pump oxygenerator if this pressure proves to be too high. Pulmonary damage during open heart operations in most cases has been due to temporary overfilling of the pulmonary vascular bed with blood, leading to capillary damage.

PULMONARY COMPLICATIONS

Once the hypothesis was accepted that short periods of overloading of the pulmonary circulation can initiate capillary damage in the lungs and thereby initiate a sequence of serious events, every attempt was made to avoid any overloading, however short its duration. The results have led to virtual elimination of pulmonary complications at the Cleveland Clinic.

Sudden overloading of the pulmonary vascular bed with blood usually occurs by a combination of (1) forward overfilling; (2) through collateral vessels; (3) retrograde overfilling.

Forward overfilling of the pulmonary vascular bed can be avoided by the following measures: (1) Rigid maintenance of a constant volume of the heart-lung machine will permit increase of the patient's blood volume only by intentional transfusion. (2) Irregularities in venous outflow can be avoided by the use of a venous reservoir in which a slight (4 mm. Hg) negative pressure is automatically maintained or by the use of an open venous reservoir that can be moved up and down so that the degree of suction can be regulated by the height of the siphon. (3) Monitoring of central venous pressure through a polyethylene tube introduced via the saphenous vein into the inferior vena cava reflects the patient's blood volume immediately.

Dynamic impediment to the outflow of the lungs is often overlooked. This impediment may occur when there is ventricular fibrillation or an ineffective left ventricular beat. When the patient is returned to his own circulation the right ventricle may have developed a more effective beat against the pulmonary arterial pressure than has the left ventricle against the higher pressure in the aorta; high pressures measured in the left atrium indicate that this may occur during the first 8 minutes after arrest with potassium citrate.

A large cannula in the left atrium can prevent retrograde overfilling except when there is obstruction of a pulmonary vein. A simple saline- or blood-filled manometer connected to the cannula will indicate the pressure in the left atrium. If a connection is opened to the venous reservoir which is under the level of the heart, a constant flow of bright red blood may be observed, and all danger of pulmonary capillary damage is immediately averted.

* KOLFF, W. J., EFFLER, D. B. and GROVES, L. K. A review of four dreaded complications of openheart operations. Causes, avoidance, and treatment of acidosis, overoxygenation, heart-block, and pulmonary damage. *Brit. Med. J.*, 5180: 1149, 1960.

College News

PRESIDENT'S COLUMN

An Inverse Parkinson's Law?

DURING THIS YEAR as I am involved in the Presidency of this College, I have become aware of the first scientific evidence that Parkinson's Law did not always hold true, that indeed there was possibly an *inverse* Parkinson's Law. This suggestion is obviously contrary to every prevailing social trend of our time and I think it important to place this case history in the literature.

To review the literature, Parkinson's Law relates to the nature of organization and defines the simple fact that as the size of an organization grows by the arithmetic progression, 1, 2, 3, 4, 5, etc., the bureaucracy responsible for it grows by the geometric progression, 2, 4, 8, 16, 32, etc., and the time must come when the organization must disappear, as its members are consumed by its bureaucracy. That this is true seems confirmed by simple observation of this *laboratory* in which we all live. In fact, one problem has been that no controls have been possible; all attempts to set up committees to study this have required additional committees which have required additional committees, etc. To come to the case at hand, this College at the end of its first active year had 297 members, 360 attended the Annual Meeting, and the employed bureaucracy totaled one individual. At its fifth year, the case under discussion had 1,458 members, 551 attended the Annual Meeting, and the employed bureaucracy was still 2.5 individuals. And, believe it or not, at its current tenth anniversary, the case in point had 2,058 members, 1,672 attended the Annual Meeting and the employed bureaucracy had swelled to 3.5 individuals.

This total divergence from scientific law is alarming and the facts become even more suspect when one studies the expected changes in the ECG (in this instance, ECG represents "extra cash garnered"). Instead of the usual changes in the ECG, with a rapidly rising S-GOT ("sorry—greater overhead today"), we find in this unusual case that the ECG and S-GOT have been absolutely stable and the fee for admission and the annual dues have been unchanged through the years . . . and yet the College has a healthy, secure fiscal report. Forgive this padding of the literature but the facts seem to warrant reporting this challenging case history.

E. GREY DIMOND, M.D.
President

PUBLISHER'S INFORMATION PAGE

The Editors and Publishers of THE AMERICAN JOURNAL OF CARDIOLOGY welcome concise articles on new findings in cardiology. As is customary in professional publications, statements in articles are the responsibility of the authors; articles must be contributed solely to THE AMERICAN JOURNAL OF CARDIOLOGY; material is copyrighted and may not be reproduced without permission of the publishers.

Preparation of Manuscripts

Authors are requested to follow these instructions carefully in preparing manuscripts: Please double space with good margins; type on one side of the sheet only; make a carbon copy for yourself and send the original with one carbon copy to the editor; include full name, degrees, staff position and affiliation; list bibliographic references in numerical order as referred to in text at the end of the article (not in footnotes). Please make certain each reference contains the name of author with initials; title of article; name of periodical with volume, page and year. For example: LEV, M. and ROWLATT, U. F. Pathology of mixed levocardia. A review of thirteen cases of atrial or ventricular inversion with or without corrected transposition. *Am. J. Cardiol.*, 8:216, 1961.

Preparation of Illustrations

So that your article will be presented most effectively, illustrations must be glossy prints or professional drawings in black ink (never in blue; it will not reproduce well). All printing on illustrations should be done professionally or with heavy type. Reference to all illustrations should be inserted in the text in consecutive order. Please follow these identification instructions: Write the figure number and the author's name on the back of each illustration and indicate the top.

Type legends for illustrations on a separate sheet with numbers corresponding to those on the photographs or drawings. Please do not attach legends to the pictures.

A reasonable number of illustrations are supplied free of cost; we know the authors will understand that special arrangements must be made with the publishers for excess illustrations and tables.

Reviews, Abstracts

Books for review may be sent directly to the Editor, Simon Dack, M.D., **The American Journal of Cardiology,** 466 Lexington Avenue, New York 17.

Permission to abstract must be obtained from the publisher. Only paid circulation journals will be permitted to abstract.

Reprints

Orders for reprints of articles should be sent directly to the Publisher, **The American Journal of Cardiology,** 466 Lexington Avenue, New York 17, New York. Prices are quoted after articles are published.

The American Journal of Cardiology
466 Lexington Avenue, New York 17, New York

Schering

life is normal again for the hypertensive on

Naqua®
trichlormethiazide

Often the only therapy needed to control blood pressure and relieve symptoms... potentiates other antihypertensives when used adjunctively ...minimal side effects... economically priced.

For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, N. J. s-868

she wakes refreshed

morning dose controls blood pressure all day

her food tastes better
(thanks to salt liberalization)

edema relieved
(shopping easier)

"cardiac fears" allayed
(zest for life returns)

NEW BOOKS FOR CARDIOLOGISTS

as listed in our new 1961-62 Catalog

(Send for a copy today)

☐ *Richard Lee Bernstine*—**FETAL ELECTROCARDIOGRAPHY AND ELECTROENCEPHALOGRAPHY.** With the improved techniques presented here, the diagnosis and treatment of fetal cardiac conditions can be immeasurably improved. *Pub.* '61, 112 pp., 139 il., $5.50

☐ *George E. Burch* and *Nicholas P. DePasquale*—**HOT CLIMATES, MAN AND HIS HEART.** The importance of relieving the diseased cardiovascular system of the burden of thermal regulation is emphasized throughout. *Pub.* '62

☐ *Donald E. Cassels* and *Minerva Morse*—**CARDIOPULMONARY DATA FOR CHILDREN AND YOUNG ADULTS.** Makes available in convenient form a wide variety of data describing the cardiac and pulmonary function of children. *Pub.* '61

☐ *E. Grey Dimond*—**THE EXERCISE ELECTROCARDIOGRAM IN OFFICE PRACTICE.** In a practical "question and answer" format Dr. Dimond describes the usefulness to the physician in private practice of the electrocardiogram obtained after exercise. *Pub.* '61, 180 pp. (11 × 8½), 338 il., $10.00

☐ *Dale Groom*—**CLINICS IN ELECTROCARDIOGRAPHY.** A cross-sectional approach to electrocardiography through actual case records and representative tracings. *Pub.* '60, 160 pp., 398 il., $8.00

☐ *William Holland* and *Richard L. Klein*—**CHEMISTRY OF HEART FAILURE.** A concise and provocative analysis of the physico-chemical mechanism of contraction in the normal and failing heart, and the mode of action of digitalis. *Pub.* '60, 132 pp., 24 il. (Amer. Lec. Living Chemistry), $5.50

☐ *Carl W. Hughes* and *Warner F. Bowers*—**TRAUMATIC LESIONS OF PERIPHERAL VESSELS.** The authors give the historical background for treatment of acute and chronic peripheral vessel lesions and trace the course of experimental development of the specialty with its various prosthetic devices to bridge vascular defects. *Pub.* '61, 208 pp., 110 il., $8.00

☐ *Richard Jones* and *Louis Cohen*—**CHEMISTRY AND THERAPY OF CHRONIC CARDIOVASCULAR DISEASE.** The authors review the chemical basis for the pathogenesis and therapy of three common complications of much chronic cardiovascular disease—congestive heart failure, thrombosis, and arteriosclerosis. *Pub.* '61, 216 pp., 63 il. (Amer. Lec. Living Chemistry), $7.50

☐ *Hans Kraus* and *Wilhelm Raab*—**HYPOKINETIC DISEASE:** Diseases Produced by Lack of Exercise. Statistical data are presented in support of the now widely accepted concept of lack of physical exercise as one of the chief contributory causes of the enormous morbidity and mortality from functional and degenerative heart disease in industrialized countries. *Pub.* '61, 204 pp., 146 il., $7.50

☐ *S. D. Larks*—**FETAL ELECTROCARDIOGRAPHY:** The Electrical Activity of the Fetal Heart. Covers the fetal ECG from the time of its earliest appearance right through the months of gestation to delivery. *Pub.* '60, 128 pp. (6¾ × 9¾), 70 il. (Amer. Lec. Gynecology and Obstetrics), $6.50

☐ *Richard H. Meade*—**A HISTORY OF THORACIC SURGERY.** "We are greatly indebted to Dr. Meade for bringing the present into better perspective with the past, and for providing this readable and highly instructive account of the development of present day concepts of surgery of the thorax."—From the Foreword by Emile Holman. *Pub.* '61, 960 pp., 117 il., $27.50

CHARLES C THOMAS • PUBLISHER 301-327 East Lawrence Avenue **SPRINGFIELD • ILLINOIS**

☐ *K. Alvin Merendino*—**PROSTHETIC VALVES FOR CARDIAC SURGERY.** Now for the first time all pertinent information on prosthetic valves is available in one source—what has been done, what is being tried, and what is being planned. *Pub.* '61, 616 pp., 393 il., $8.25

☐ *Arthur J. Moss* and *Forrest H. Adams*—**PROBLEMS OF BLOOD PRESSURE IN CHILDHOOD.** The authors emphasize particularly recommended techniques, the interpretation of results, and the range of normal values. *Pub.* '61 (Amer. Lec in Pediatrics)

☐ *George White Pickering et al.*—**THE TREATMENT OF HYPERTENSION.** Provides crucial criteria for clinical differentiation between benign and malignant states. *Pub.* '61, 192 pp., 70 il. (Amer. Lec. Living Chemistry), $7.00

☐ *Peter Safar* and *Martin C. McMahon*—**RESUSCITATION OF THE UNCONSCIOUS VICTIM:** A Manual for Rescue Breathing (2nd Ed.). An important addition to the Second Edition is an illustrated description of the new method of closed chest cardiac massage for cases of circulatory failure. *Pub.* '61, 100 pp., 36 il., $2.00

☐ *Hans Selye*—**THE PLURICAUSAL CARDIOPATHIES.** Once again medical history is made with the publication of Dr. Selye's most recent original and previously unpublished observations—observations which show that many diseases of the heart are caused, not by any one pathogen, but by complex pathogenic situations. *Pub.* '61, about 492 pp., about 287 il. (2 in full color), $21.00

☐ *Jaques B. Wallach* and *Edgar F. Borgatta*—**RHEUMATIC HEART DISEASE:** Pathology and Clinical Implications—A Summary of Five Hundred Nine Autopsied Cases. This is the most complete tabular summary available of such important data as incidence of rheumatic heart disease, frequency of involvement of each valve, relation to death of the patient, complicating lesions, sex, age, as well as the various inter-relationships of these factors. *Pub.* '61

☐ *Sigmund Adam Wesolowski*—**EVALUATION OF TISSUE AND PROSTHETIC VASCULAR GRAFTS.** In this unique study Dr. Wesolowski evaluates all presently used vascular graft materials and places their selection on a scientific basis. *Pub.* '61, about 181 pp. ($6^3/_4 \times 9^3/_4$), about 88 il. (Amer. Lec. Surgery)

☐ *Merle E. White*—**AN OUTLINE GUIDE FOR THE CARE OF POST-OPERATIVE CARDIAC PATIENTS.** After reading this book your nurses will take greater pride in being part of a cardiac team and will be more impressed with their own important role in the drama of hope for the diseased heart. *Pub.* '61, 120 pp, 75 il., $6.00

☐ *W. Carleton Whiteside*—**TOWARD THE DIAGNOSIS OF CONGENITAL HEART DISEASE.** A summary, closely screened, of recent proven authoritative literature by those best qualified to write on the signs and symptoms of congenital cardiac defects—a guide to lesions of the youthful heart. *Pub.* '60, 100 pp., $4.50

☐ *S. E. Wright*—**THE METABOLISM OF CARDIAC GLYCOSIDES:** A Review of the Absorption, Metabolism and Excretion of Clinically Important Cardiac Glycosides. ". . . represents essential reading for anyone interested in the pharmacology of digitalis."—*The American Journal of Cardiology*. *Pub.* '60, 94 pp., 14 il. (Amer. Lec. Biochemistry and Biophysics), $4.75

☐ *Grace Wyshak et al.*—**CARDIACS AND DIABETICS IN INDUSTRY:** A Study in Work Experience. Presenting the first truly objective study comparing the work experience of 709 persons with cardiovascular disease or diabetes with that of 709 matched controls who were free from these diseases. *Pub.* '61, about 264 pp., about 36 il.

☐ *Benjamin W. Zweifach*—**FUNCTIONAL BEHAVIOR OF THE MICROCIRCULATION.** A primer of basic knowledge to facilitate an understanding of modern principles of blood-tissue exchange, tissue injury, and systemic disturbances such as shock and hypertension. *Pub.* '61, 164 pp., 20 il. (Amer. Lec. Physiology), $7.00

CHARLES C THOMAS • PUBLISHER 301-327 East Lawrence Avenue **SPRINGFIELD • ILLINOIS**

IN SHOCK OF MYOCARDIAL INFARCTION

INJECTION

ARAMINE®

(metaraminol)

"...A strong pressor effect with a myocardial-stimulating action in experimental studies."[1] "...Tens of thousands of intramuscular and subcutaneous injections. ... Not a single instance of tissue injury was observed."[2]

ARAMINE can be administered for pressor effect by any route—subcutaneous, direct intravenous, intramuscular, intravenous infusion. No slough reported **when injected into preferred vein of arm.** Minimal risk of causing arrhythmias.

Onset of action (intravenous): 1 to 2 minutes.

ARAMINE is always ready for immediate use—no dilution needed.

ARAMINE is also valuable in shock accompanying anaphylaxis, brain damage, infectious disease, hemorrhage, surgery, trauma.

Supplied: In 1-cc. ampuls and 10-cc. vials (10 mg. metaraminol present as the bitartrate per cc.).

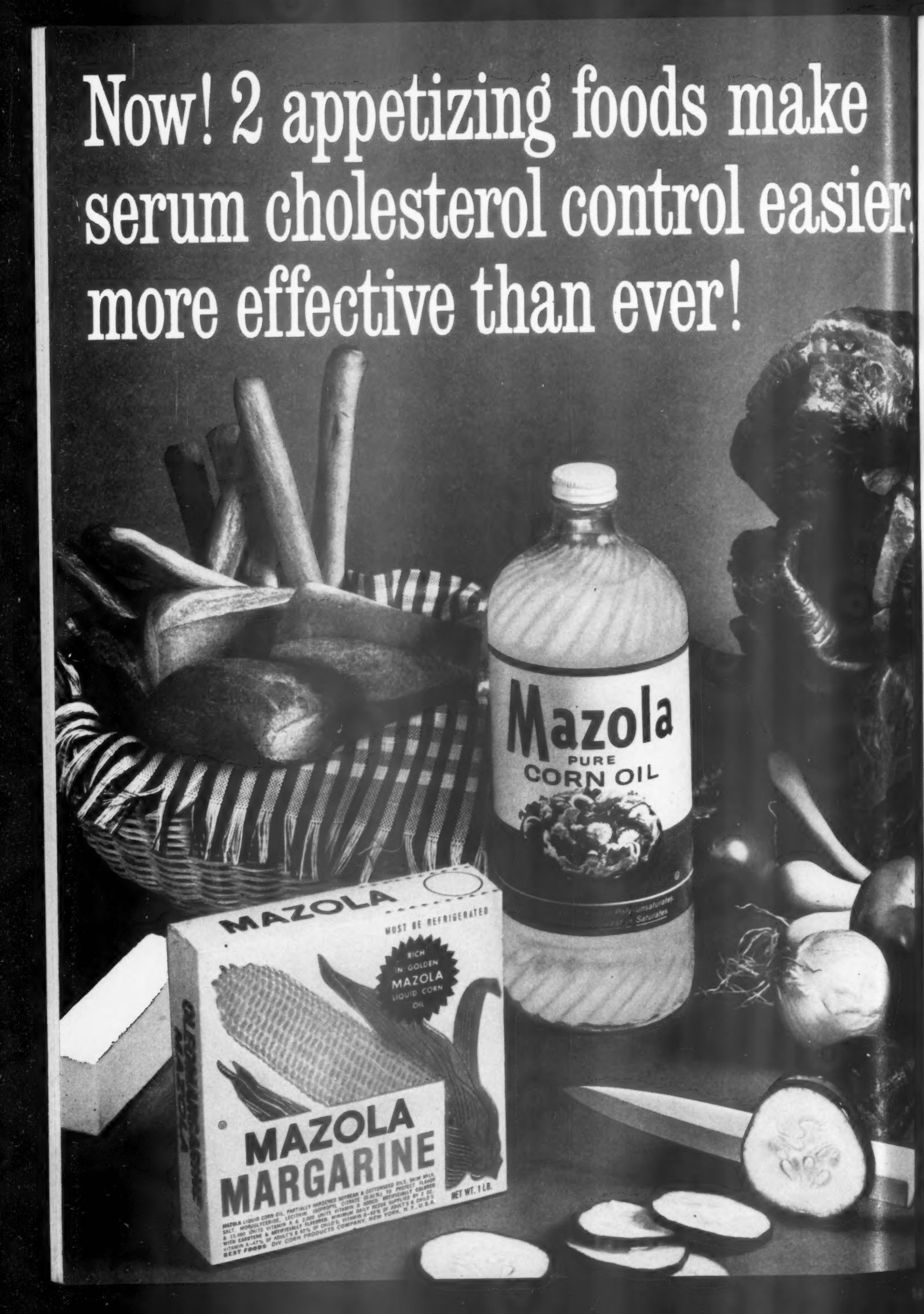
ARAMINE is a trademark of Merck & Co., INC.

Additional information is available to physicians on request.

1. Selzer, A., and Rytand, D. A.: COUNCIL ON DRUGS, Report to the Council, J.A.M.A. 168:762 (Oct. 11) 1958.

2. Weil, M. H.: J.A.M.A. 171:1868, (Nov. 28) 1959.

MSD MERCK SHARP & DOHME, Division of Merck & Co., INC., West Point, Pa.


Now! 2 appetizing foods make serum cholesterol control easier, more effective than ever!
Mazola
PURE
CORN OIL
MAZOLA
MUST BE REFRIGERATED
RICH IN GOLDEN MAZOLA LIQUID CORN OIL
MAZOLA
MARGARINE
NET WT. 1 LB.

r.

Le
ru
ex
be
Pe
ar
in
an
M
in
hy
ap
M

Your Patients Can Enjoy Fine Foods With Minimum Diet Changes!

For good eating while maintaining serum cholesterol control

Leading authorities agree that where reduction of serum cholesterol levels is indicated, fat intake should not exceed ⅓ of total calories and of this, at least ⅓ should be polyunsaturated fats.

Polyunsaturated fats, such as those found in corn oil, are rich in the linoleates which are important in reducing serum cholesterol levels. This has been proven time and again in nutritional studies of hypercholesterolemia. Mazola Margarine and Mazola Corn Oil have outstanding P/S (polyunsaturate to saturate) ratios. Thus the hypercholesterolemic patient can usually enjoy the same appetizing foods as the rest of the family.

Mazola Corn Oil is unexcelled in polyunsaturates and lowest in saturates of all leading brands of vegetable oils. Mazola's P/S ratio is far higher than that of any other leading food oil. Your patient will find Mazola Corn Oil ideally suited for salad dressings and frying; also for baking wherever *liquid* shortenings are called for in the recipe.

Mazola Margarine* contains *liquid* Mazola Corn Oil as a major ingredient. This corn oil is not hydrogenated, thereby preserving its rich content of linoleates. Mazola Margarine contains 2 to 3 times as much natural linoleates as any other margarine readily available in grocery stores from coast to coast. Its taste, color and handling characteristics are unexcelled.

*U.S. Pat. No. 2,955,039

AVERAGE COMPOSITIONS OF MAZOLA® MARGARINE AND MAZOLA® CORN OIL

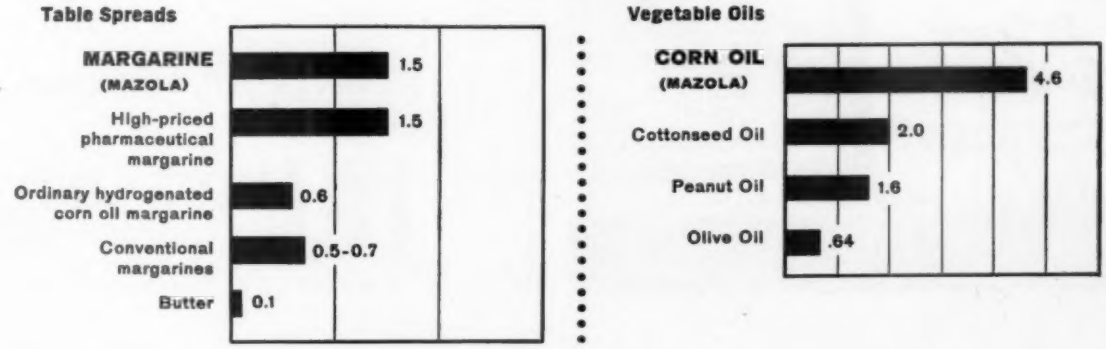
(All figures are in grams.)

	MAZOLA MARGARINE		MAZOLA CORN OIL	
	100 grams	2 oz. (4 tbsp.)	100 grams	1 fl. oz. (2 tbsp.)
Fatty Acids				
Polyunsaturated	21	12	51	14
Monounsaturated	40	23	32	9
Saturated	14	8	11	3
Natural Sitosterols	0.5	0.3	1	0.3
Natural Tocopherols	0.08	0.045	0.08	0.020
Cholesterol	none	none	none	none
Sodium	0.9	0.5	none	none

MAZOLA MARGARINE—410 Calories/2 oz.; Iodine Value—96
MAZOLA CORN OIL—250 Calories/fl. oz.; Iodine Value—124

RATIO OF POLYUNSATURATES/SATURATES

(Average values.)



CORN PRODUCTS COMPANY 10 East 56th Street, New York 22, N.Y.

coronary insufficiency?

provide prompt *and*

prolonged protection with...

'Cardilate'

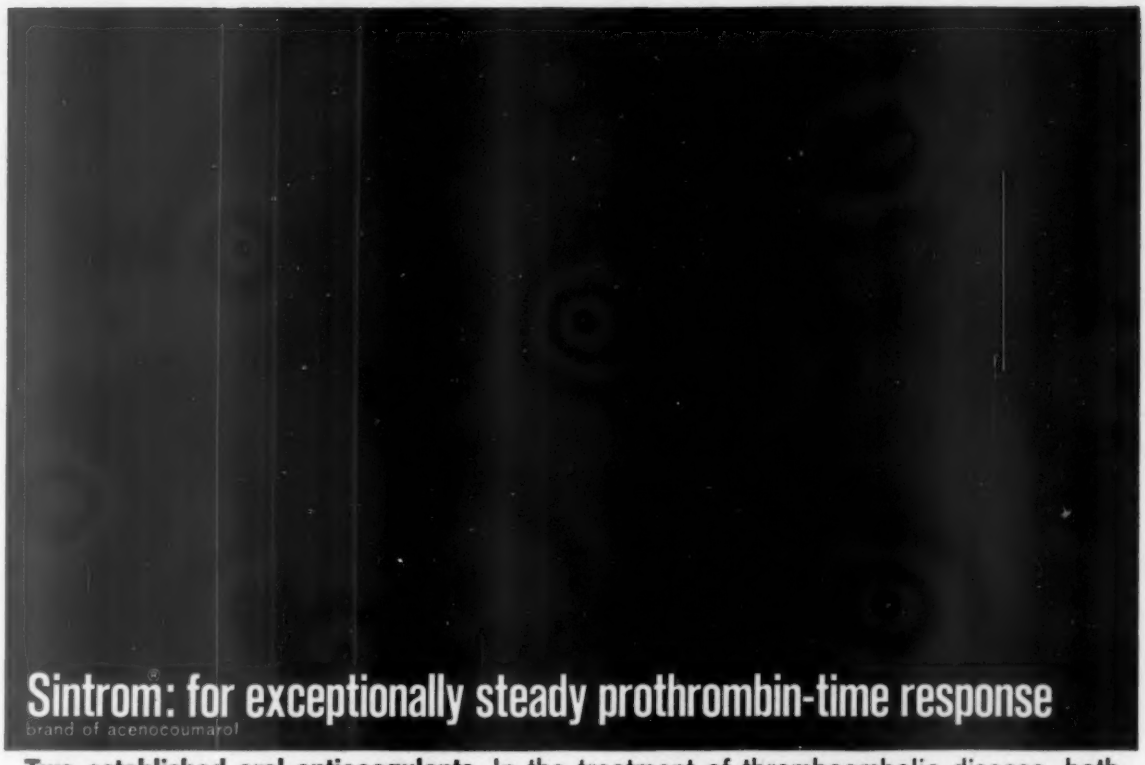
brand

ERYTHROL TETRANITRATE

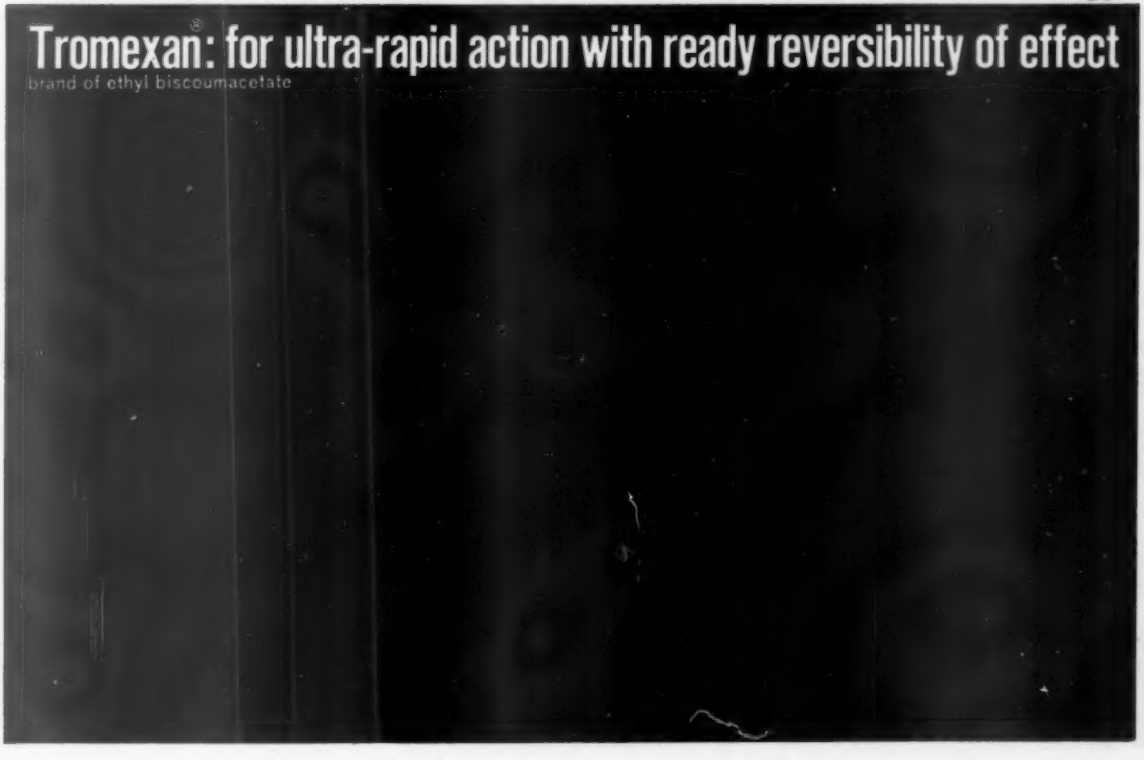
in angina: "Because of its rapid action... it may be used like nitroglycerin before contemplated exertion or excitement when more prolonged prophylaxis is desired." Russek, H. I.: Am. J. M. Sc. *239*:478, 1960.

Tablets of 5 mg. and 15 mg. Literature available on request.

BURROUGHS WELLCOME & CO. (U. S. A.) INC., Tuckahoe, N. Y.



Two established oral anticoagulants. In the treatment of thromboembolic disease, both Sintrom and Tromexan reliably bring about hypoprothrombinemic response.
Distinguished by high potency and its ability to maintain a uniform response with a constant single daily dose, Sintrom is particularly suited to long-term therapy. Significantly more rapid and transient in action, Tromexan is well adapted to cases calling for more immediate control of thrombotic tendencies.
Full information regarding dosage, side effects, precautions and contraindications available on request.
Sintrom®, brand of acenocoumarol, is supplied as double-scored tablets of 4 mg.
Tromexan®, brand of ethyl biscoumacetate, is supplied as single-scored tablets of 150 and 300 mg.
Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Ardsley, New York SI/TR-662-61 **Geigy**



REPRINT ORDER FORM

THE AMERICAN JOURNAL OF MEDICINE
466 Lexington Ave.,
New York 17, N. Y.

Please send me the following reprints from THE AMERICAN JOURNAL OF MEDICINE.

SEMINARS

☐	ALLERGY (1956)	$2.00
☐	DISEASES OF THE PANCREAS (1956)	$2.00
☐	LIVER DISEASE (1958)	$2.00
☐	MYCOTIC INFECTIONS (1959)	$3.00
☐	RENAL PHYSIOLOGY (1950)	$2.00

Enclosed is my check

Name_____

Address_____

City_____ State_____

Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltrate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: **1.** Ellis, L. B. *et al.*: Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.*: Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

CML-3619

Miltrate®

Miltown® (meprobamate) + PETN

WALLACE LABORATORIES / *Cranbury, N. J.*

For the unique advantages of permanent, immediately visible inkless recordings in true rectangular coordinates—in applications ranging from cardiac catheterization and pharmacological studies to student physiology laboratory work — the wide variety of combinations and choices offered by Sanborn direct writers provides an almost "custom designed" system for your particular needs.

The proven reliability and simplicity of tube circuits, in 1- to 8-channel systems with a wide choice of interchangeable plug-in preamplifiers, horizontal chart plane and system frequency response to 100 cps, are offered by the widely-used "150" Series. For *extended frequency response, greater compactness* and other advantages of solid state circuitry in *applications up to 4 channels*, the new "964" system (4 channels) and the new 296T (2 channels) combine the most modern electronic design features with simple, economical cabinet packaging. When the *greatest possible versatility* in *5 to 8 channels* are required, "350" Series systems provide the maximum performance and flexibility of all Sanborn direct writers. Flush front recorder has vertical chart plane, and a wide choice of interchangeable preamplifiers. For *portability in 1- and 2-channel systems*, Models 299, 301, 320, 321 and 322 are compact, modern, lightweight units designed to handle a wide variety of applications.

For complete information on these systems, call your nearest Sanborn Branch Office or Service Agency, or write Manager, Research Instrument Sales, Medical Division.

MEDICAL DIVISION
SANBORN COMPANY
175 Wyman St., Waltham 54, Massachusetts

NEW 8th EDITION

MODERN DRUG ENCYCLOPEDIA

and Therapeutic Index with monthly supplement MODERN DRUGS

The only complete reference on new as well as established products.

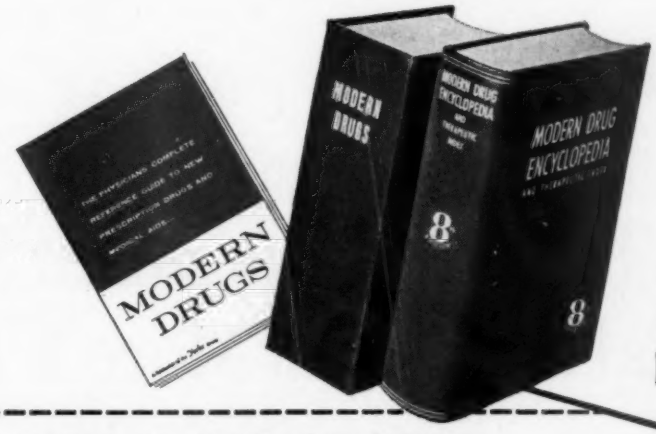
Quickly answers questions about ethical pharmaceuticals.

MODERN DRUG ENCYCLOPEDIA, 8th Edition, an authoritative source of information on new and established pharmaceuticals. Gives you pertinent *facts* in concise form. Supplies facts you want to know to prescribe the new products with confidence. No struggle to keep cumbersome files up to date—just one compact bound volume and a compact binder for the monthly supplements.

MODERN DRUGS

A monthly supplement, with Robert S. Goodhart, M.D. as supervising editor, and John C. Helenore, Ph.G. as technical editor, supplies the same complete information on *new* pharmaceuticals as soon as they are available on your prescription. A convenient binder keeps the 24 issues together. Cumulative indices in *each* issue help you find *any* product listed in previous months.

THE PHYSICIAN'S REFERENCE LIBRARY IN ONE VOLUME KEPT UP-TO-DATE MONTHLY



ORDER YOUR MODERN DRUG ENCYCLOPEDIA TODAY

The Reuben H. Donnelley Corp., Publisher
MODERN DRUG ENCYCLOPEDIA
466 Lexington Avenue, New York 17, N.Y.

☐ Enclosed is $17.50* for my 8th Edition of MODERN DRUG ENCYCLOPEDIA and Therapeutic Index and the Monthly Supplement—MODERN DRUGS.

☐ Enclosed also is $3.50 for binder for MODERN DRUGS Monthly Supplement.

For delivery in N.Y.C., please include 3% Sales Tax with remittance.

Name_____

Address_____

City_____ Zone_____ State_____

U.S.A. $17.50 Foreign $23.50 (U.S. Currency)

Please make checks payable to The Reuben H. Donnelley Corporation

*Includes 2-year supplementary service at $5.00 per year ($6.00 Foreign)

No. 1 **of a series reporting on Endo Laboratories' Anticoagulant Survey**

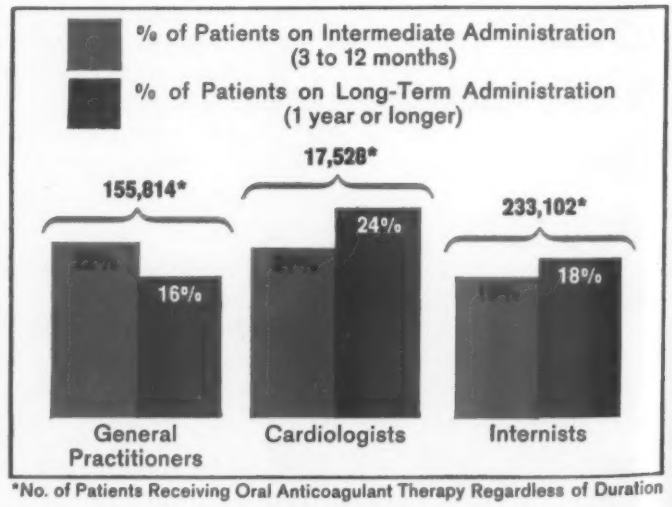
Nationwide Survey Explores Current Practices in Anticoagulant Therapy

Early in 1961 Endo Laboratories undertook a comprehensive survey of physicians' attitudes toward oral anticoagulants and their application in daily practice. Approximately 90,000 physicians received a questionnaire which covered such basic matters as *when, how,* and *for what periods* anticoagulants were used, the *specific advantages* of the agent most often selected by general practitioners, internists, and cardiologists, *factors* relating to the effective, safe administration of anticoagulants, and other pertinent areas of clinical interest. A total of 10,016 physicians completed and returned the *Anticoagulant Survey*.

The vast accumulation of data has now been analyzed and tabulated so that one can draw conclusions regarding the actual practice of thousands of physicians. Endo is happy to present the findings of *Anticoagulant Survey* in the first of a series of brief reports. It is our purpose thereby to contribute to a better understanding of the use of anticoagulants, therapeutically and prophylactically. We would greatly appreciate your comments and observations on this series. For more detailed information on *Anticoagulant Survey*, write to the Professional Service Dept., Endo Laboratories, Richmond Hill 18, New York.

Long-Term Anticoagulant Therapy of Myocardial Infarction More Widely Accepted

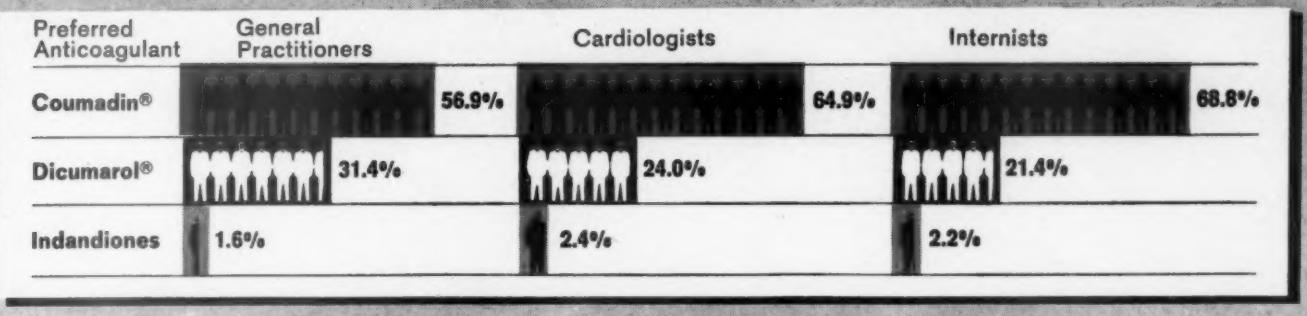
Broad clinical experience[1-12] has indicated the value of oral anticoagulants in preventing or minimizing the occurrence of myocardial infarctions and extending life expectancy, particularly on long-term use. Reports from general practitioners and specialists reveal that these life-saving agents are being used *prophylactically* not only after frank myocardial infarction but also in *impending* infarction associated with angina pectoris. The following table shows the percentage of patients who have been maintained on oral anticoagulant therapy for extended periods of time, according to replies of physicians who answered the Endo anticoagulant questionnaire.



*No. of Patients Receiving Oral Anticoagulant Therapy Regardless of Duration

Specialists and General Practitioners Using Coumadin Increasingly

A comparison of Coumadin (warfarin sodium), Dicumarol (bishydroxycoumarin), and Indandiones showed that coumarin derivatives were prescribed most often and that Coumadin was the drug of choice by a wide margin.



It is noteworthy that 80% of the general practitioners, 80% of the internists, and 86% of the cardiologists favoring Coumadin reported their use of oral anticoagulants to be **increasing.** Of 3,092 responding physicians in general practice, 564 had had patients on Coumadin for one year, 628 for two years, 479 for three years, 215 for four years, 181 for five years, and 149 for **more than five years.**

Specialists Favor Tapering Anticoagulant Dosage Before Discontinuance

Abrupt cessation of anticoagulant therapy, especially after long-term administration, has been cautioned against by some clinicians[5,12] because of the possibility of a consequent state of *hypercoagulability* with increased risk of thromboembolism. *Anticoagulant Survey* showed that of the general practitioners who stated their procedure more than half did *not* taper the dose before discontinuance; on the other hand, a majority of internists and cardiologists did taper the dose over several weeks.

Periodic Prothrombin Time Tests Essential to Effectiveness and Safety

Especially in long-term therapy, *periodic prothrombin time determinations* are recognized as vital to effectiveness and safety. Most of the reporting physicians are having these tests performed at one-week, two-week, or four-week intervals. The following data from *Anticoagulant Survey* indicate that the predominant trend is toward testing at intervals of two weeks or longer, and that this procedure is observed by a significantly higher percentage of reporting physicians who prefer Coumadin than by those who favor Dicumarol.

Preferred Anticoagulant	PT Tests Every Week		PT Tests Every 2 to 4 Weeks or Longer	
	GP's	Specialists	GP's	Specialists
Coumadin	17%	16%	63%	67%
Dicumarol	27%	23%	55%	60%

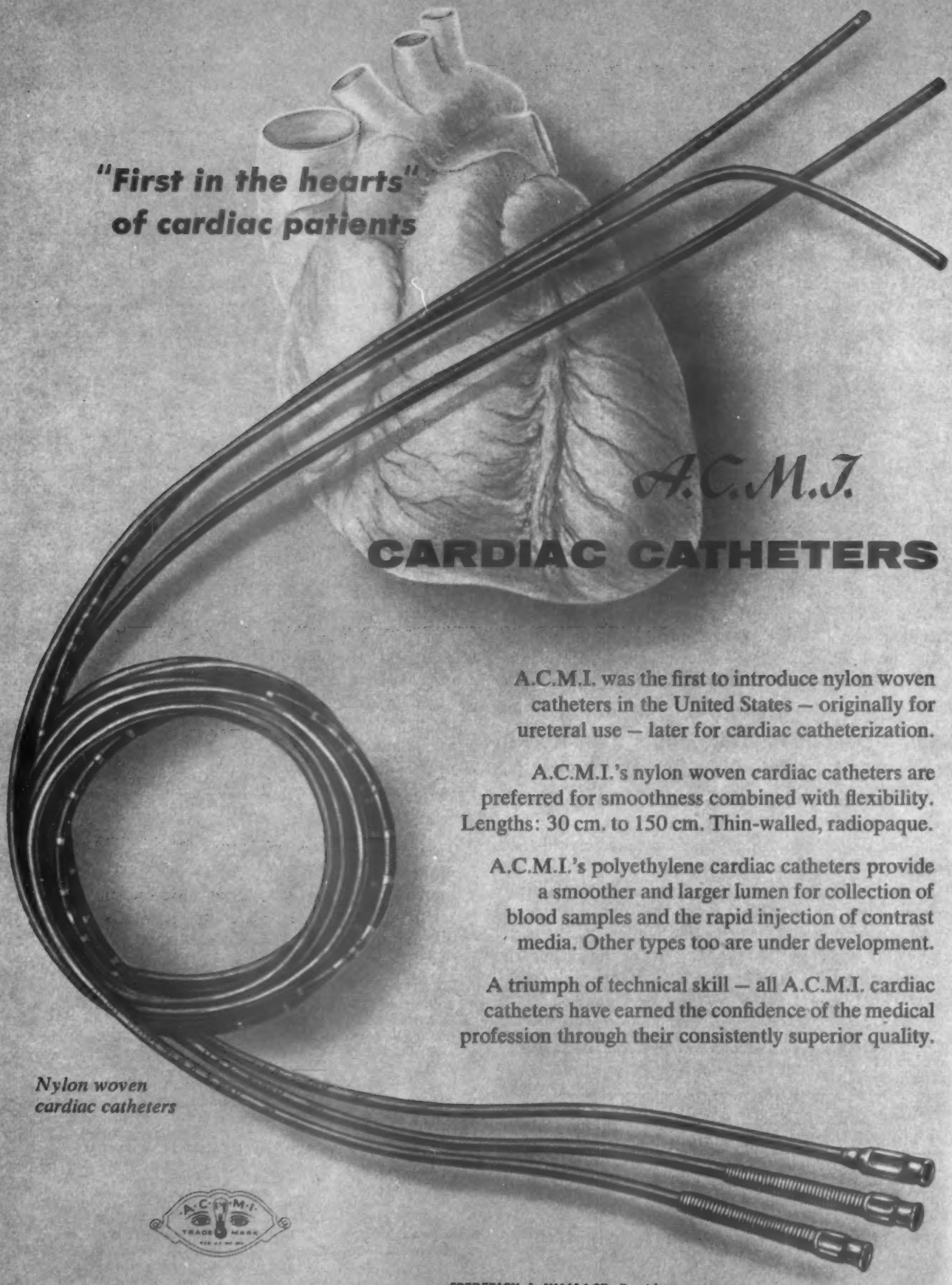
The preferred prothrombin time range was between 1½ to 2½ times normal control; the most favored prothrombin time was twice normal, or 26 seconds. (Complications of anticoagulant therapy will be discussed in a subsequent report.)

Physicians Stress Predictability and Ease of Maintenance in Selecting Anticoagulant

In characterizing the *advantages* of the oral anticoagulant most often prescribed (Coumadin), general practitioners, cardiologists, and internists were unanimous in listing, in order of importance: (1) *more predictable effect*, (2) *easier maintenance*, and (3) *single daily dose*. Among Dicumarol prescribers, on the other hand, "single daily dose" was first in importance, "more predictable effect" second, and "easier maintenance" third.

These data confirm the unusually consistent recognition of Coumadin advantages which have made possible a smoother, more easily managed long-term anticoagulant regimen. Since Coumadin may be given I.M. and I.V. as well as orally, it is also the most versatile of anticoagulants in hospital or office practice.

References: 1. Thomes, A. B., et al.: J.A.M.A. 176:181, 1961. 2. Nora, J. J.: **Ibid.** 174:118, 1960. 3. **Idem:** M. Times 89:502, 1961. 4. Beamish, R. E., and Storrie, V. M.: Heart Bull. 10:41, 1961. 5. Nichol, E. S., et al.: Am. Heart J. 55:142, 1958. 6. Manchester, B.: Ann. Int. Med. 47:1202, 1957. 7. Report of Working Party on Anticoagulant Therapy in Coronary Thrombosis to M. Res. Council: Brit. M. J. 1:803, 1959. 8. Friedberg, C. K.: New York J. Med. 58:877, 1958. 9. Seaman, A. J.: GP 22:135, No. 4, 1960. 10. Stephens, C. A. L., Jr.: Arizona Med. 17:499, 1960. 11. Canady, E. W., et al.: Illinois M. J. 113:50, 1958. 12. Littman, M. L.; Barrett, E. A., and Shapiro, S.: Scientific Exhibit, 110th Annual Meet., A.M.A., New York, N. Y., June 25-30, 1961.



"First in the hearts"
of cardiac patients

A.C.M.I.

CARDIAC CATHETERS

A.C.M.I. was the first to introduce nylon woven catheters in the United States – originally for ureteral use – later for cardiac catheterization.

A.C.M.I.'s nylon woven cardiac catheters are preferred for smoothness combined with flexibility. Lengths: 30 cm. to 150 cm. Thin-walled, radiopaque.

A.C.M.I.'s polyethylene cardiac catheters provide a smoother and larger lumen for collection of blood samples and the rapid injection of contrast media. Other types too are under development.

A triumph of technical skill – all A.C.M.I. cardiac catheters have earned the confidence of the medical profession through their consistently superior quality.

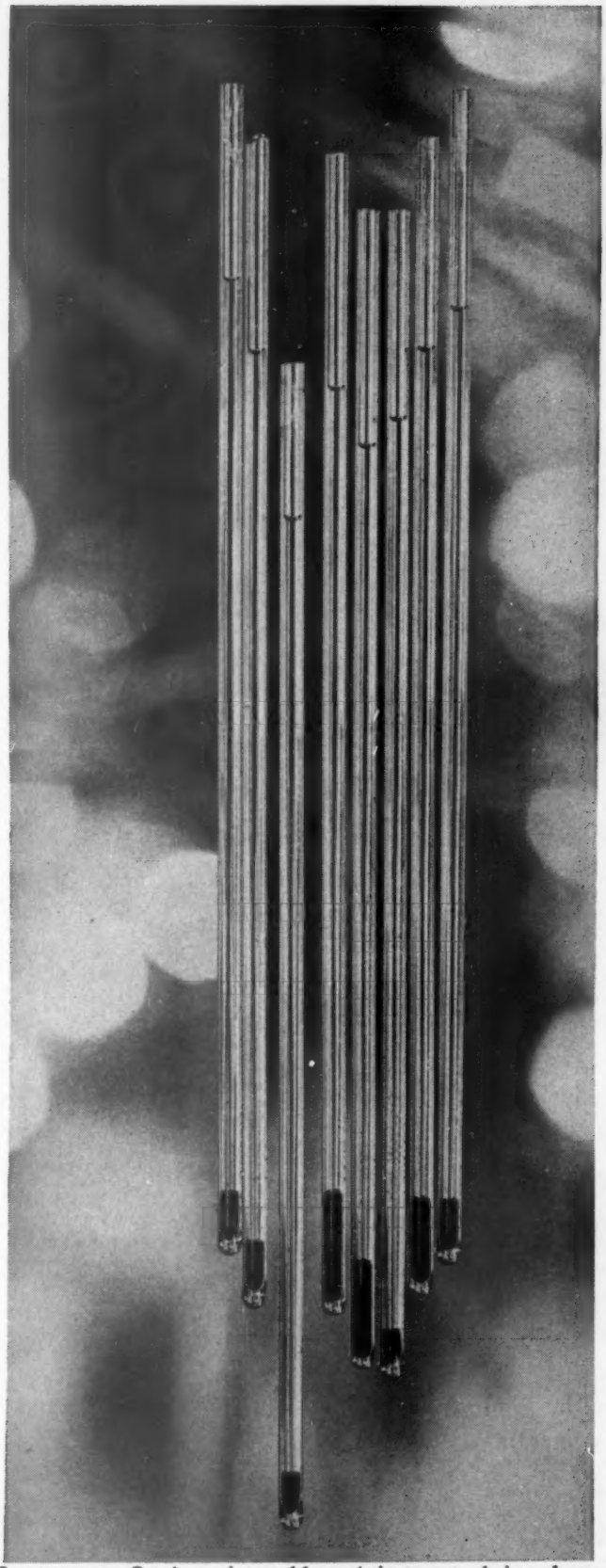
Nylon woven cardiac catheters

A·C·M·I·
TRADE MARK

FREDERICK J. WALLACE, *President*

American Cystoscope Makers, Inc.

8 PELHAM PARKWAY, PELHAM MANOR, N. Y.



IMMUNOCRIT® tubes, pictured here 4 times actual size, show results of centrifuging patients' serums with BETA-L TEST antiserum. Longest columns of precipitate indicate high beta-lipoprotein levels.

NEW...

A SPECIFIC SIMPLE INEXPENSIVE TEST FOR ESTIMATING SERUM BETA-LIPOPROTEIN LEVELS

BETA-L TEST™

The growing evidence implicating beta-lipoprotein as one of the agents responsible for atherosclerosis has emphasized the need for a test procedure which is reliable, yet simple enough to be suited to clinical purposes.[1] Hyland BETA-L TEST answers this need. BETA-L TEST results show a close correlation with complex quantitative methods now in use, yet BETA-L TEST can be performed in ten minutes on one drop of serum and employs a minimum of laboratory equipment and technical skill.[2]

The resulting economy and simplicity provide you with a reliable routine screening test and make frequent serial determinations of beta-lipoprotein practical for the first time.

When ordering your next beta-lipoprotein determinations, specify Hyland BETA-L TEST. Materials for BETA-L TEST are now available to your laboratory in 60-test kits.

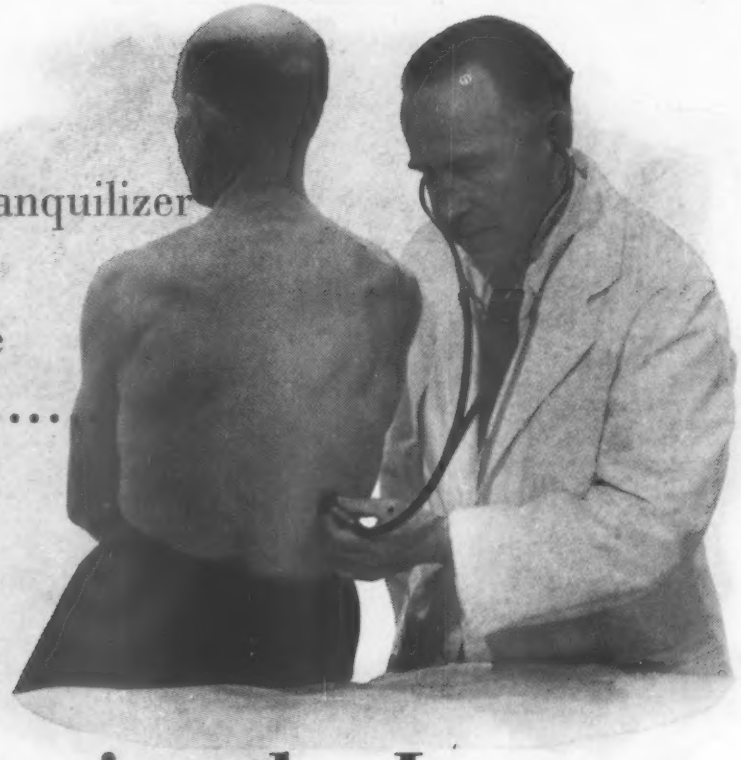
1. Wood, F. C., Gurin, S., and Kuo, P. T.: Medical Correlation Clinic on Atherosclerosis and Coronary Artery Disease, Am. Pract.–Dig. Treat. *12:* 235 (April) 1961.
2. Heiskell, C. L., Fisk, R. T., Florsheim, W. H., Yachi, A., Goodman, J. R., and Carpenter, C. M.: A Simple Method for Quantitation of Serum Beta-Lipoproteins by Means of the Immunocrit, Amer. J. Clin. Path. *35:* 222 (March) 1961.

Hyland

HYLAND LABORATORIES

4501 Colorado Blvd.,
Los Angeles 39, California
Branch Office: 160 Lockwood Ave., Yonkers, N.Y.

New
diuretic-tranquilizer
for
congestive
failure.....



Drains the Lungs ...Calms the Fear

and helps the patient breathe

Miluretic combines hydrochlorothiazide and Miltown in a single tablet — making the treatment of congestive failure simpler for you and cheaper for the patient.

Miluretic's hydrochlorothiazide component drains the lungs of excess fluid to help the patient breathe comfortably — while the Miltown component calms the patient's fear and anxiety about his condition.

Saves the patient's money. A prescription for Miluretic is more than 20% cheaper than its two ingredients prescribed separately.

Composition: 25 mg. hydrochlorothiazide + 200 mg. Miltown (meprobamate).

Dosage: For congestive failure, 2 tablets four times a day. For hypertension, 1 tablet four times a day.

Supplied: Bottles of 50 white, scored tablets.

New
Miluretic*
HYDROCHLOROTHIAZIDE + MILTOWN®

WALLACE LABORATORIES/*Cranbury, N. J.*

*TRADE-MARK

CHY-5034

Advertisers' Product Index

September, 1961

(Continued on next page)

*** Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA**

*** Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA**

When the rhythm is wrong...PRONESTYL® HYDROCHLORIDE

"Procaine amide [Pronestyl] should be [a] drug of choice in arrhythmias of ventricular origin."[1] "Pronestyl will be [a] drug of choice for intravenous use. The intramuscular preparation of Pronestyl has a clear advantage over the intramuscular preparation of quinidine because effects develop more rapidly."[2] Pronestyl sometimes stops arrhythmias which have not responded to quinidine[3,4]. . . Pronestyl may be used in patients sensitive to quinidine . . . more prolonged action, less toxicity, less hypotensive effect than procaine . . . no CNS stimulation such as procaine may produce.

Supply: For convenient oral administration: **Capsules**, 0.25 Gm., in bottles of 100 and 1000. For I. M. and I. V. administration: Parenteral Solution, 100 mg. per cc., in vials of 10 cc. For full information see your Squibb Product Reference or Product Brief.

References: 1. Zapata-Diaz, J., et al.: Am. Heart J. 43:854, 1952. 2. Modell, W.: In Drugs of Choice, C. V. Mosby Co., St. Louis, 1950, p. 419. 3. Kayden, H. J., et al.: Mod. Concepts Cardiovasc. Dis. 20:100, 1951. 4. Miller, H., et al.: J.A.M.A. 146:1004, 1951.

SQUIBB *Squibb Quality — the Priceless Ingredient*

PRONESTYL® is a Squibb Trademark